RIKEN RESEARCH

SPRING 2024

SHOWCASING THE BEST OF JAPAN'S PREMIER RESEARCH ORGANIZATION • www.riken.jp/en/

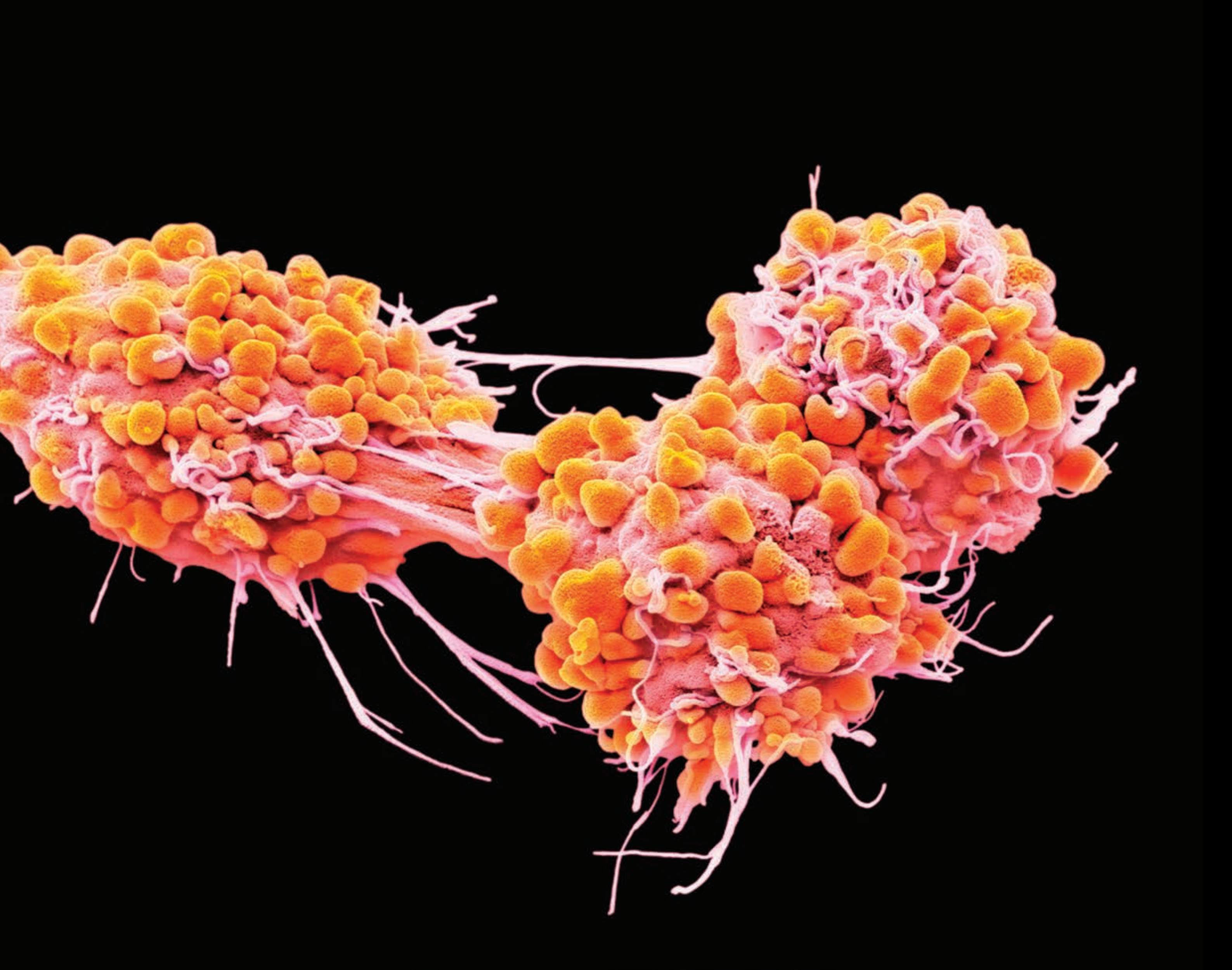
GENE SNATCHERS

Parasitic mind control via stolen DNA

BACTERIAL BOOST
Solving milk allergy in kids?

QUANTUM VORTEX
Using laser beams as very fast stirrers

LETHAL PAYLOAD
Hitting cancer where it hurts with a potent radionuclide



APPLYING BIG DATA TO OVARIAN CANCER
A colored scanning electron micrograph of ovarian cancer cells. A big-data study on the genetics of one of the deadliest forms of ovarian cancer could help to develop more effective treatments (see page 23).

RIKEN RESEARCH

RIKEN, Japan's flagship research institute, conducts basic and applied research in a wide range of fields including physics, chemistry, medical science, biology and engineering.

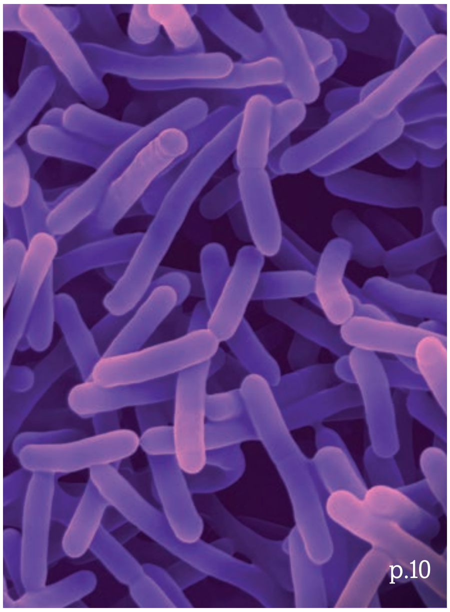
Initially established as a private research foundation in Tokyo in 1917, RIKEN became a national research and development institute in 2015.

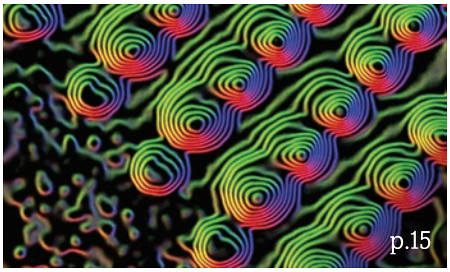
RIKEN Research is an online and print publication that highlights the best research published by RIKEN. This publication is a selection of the articles published by RIKEN at: https://www.riken.jp/en/news_pubs/research_news/ Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

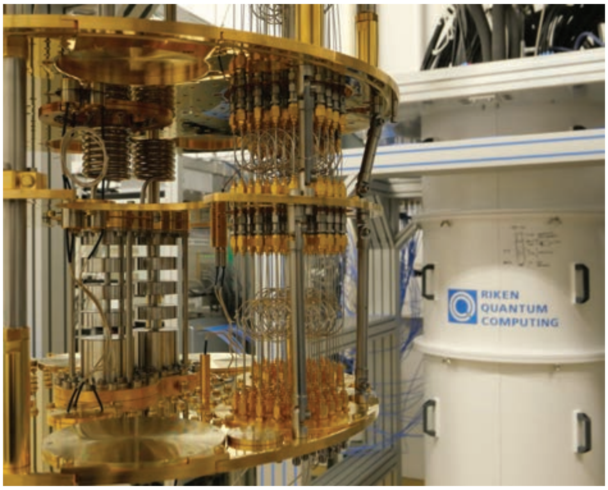
RIKEN Research is published by RIKEN in collaboration with Nature Research Custom Media, a part of Springer Nature.

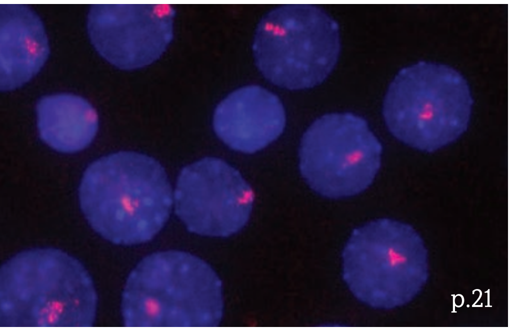
For further information on the research in this publication or to arrange an interview with a researcher, please contact:
RIKEN International Affairs Division
2-1, Hirosawa, Wako,
Saitama, 351-0198, Japan
Tel: +81 50 3500 5438
rikenresearch@riken.jp

ISSN 1883-3519
www.riken.jp/en

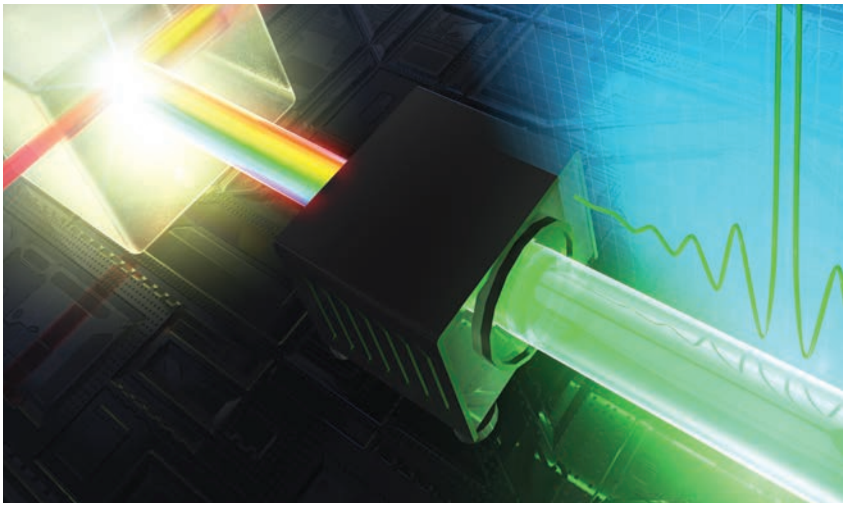

p.10

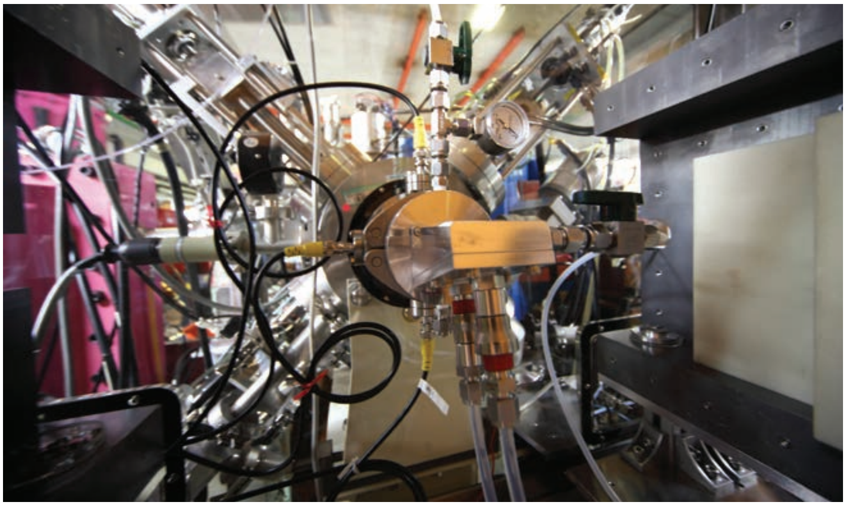

p.15


RIKEN
QUANTUM
COMPUTING



p.21





To our readers

Kohei Miyazono
Executive Director, RIKEN

In this editorial I would like to report on the 12th RIKEN Advisory Council, which was held in the middle of December in Tokyo and on our Wako campus. For us, the advisory council (informally called RAC) is an important event, which was first held three decades ago in 1993. We invited experts from around the world to review our research activities and management and to make recommendations for the future.

This time, we were fortunate to have the RAC held under the leadership of Prof. Chorh Chuan Tan, chairman of Singapore's Agency for Science, Technology and Research (A*STAR), who served as chair, and Professor Emeritus Se-jung Oh of Seoul National University and Ikuko Hara-Nishimura, Professor Emeritus of Kyoto University and Executive Director of the Nara National Institute of Higher Education and Research, who served as vice-chairs.

The members of the RAC had intensive discussions for three days, and following the meetings, presented us with a set of valuable recommendations, including evaluations of our recent activities and specific advice in areas such as our TRIP (Transformative Research Innovation Platform of RIKEN platforms) initiative, strengthening links between researchers in RIKEN, our innovation activities, diversity, and our efforts to attract outstanding researchers from around the world, in anticipation of the start of our 5th Mid- to Long-term Plan period. The RAC members finally provided us with four main recommendations to maintain RIKEN's position as a leading research institution.

I was impressed by how the members were able to quickly understand our large and complex organization and to come up with constructive guidance. Clearly, there are certain important issues that research organizations and researchers worldwide are confronting together, and I strongly felt how important it is to learn from the experiences and ideas of people from around the world.

We would like to do our best to implement the recommendations we received, and report our new achievements to the members.

宮園浩平

COVER STORY: Horizontal gene transfer might be allowing parasitic horsehair worms to manipulate their mantis hosts into jumping into water so that the worms can reproduce. *Page 17*

Keep up to date

Online
www.riken.jp/en

Facebook
facebook.com/RIKENHQ

X (formerly Twitter)
twitter.com/RIKEN_en

LinkedIn
linkedin.com/company/riken

Creating exotic superconducting phenomena

Sadashige Matsuo
Research Scientist, Quantum Functional System Research Group, RIKEN Center for Emergent Matter Science

Please describe your research.
My work is focused on seeking out exotic superconducting phenomena that could be used to control solid-state devices. We do this by designing device 'structures'. For example, when electrons are confined within a tiny device structure, we can precisely control the number of electrons in the structure.

We sometimes also focus on controlling the phenomena at the junction of two different materials.

In our recent research, we revealed new superconducting phenomena by tweaking a number of device elements: the structure, the materials, and the electrical controls.

What excites you about your research?
In my view, the most exciting point in my research is always when we manage to engineer superconducting phenomena by creating a new device structure. We do this using CAD (computer-aided design) software for the design and electron beam lithography for the fabrication.

The devices we make help provide information on superconducting phenomena peculiar to its structure, but sometimes the phenomena may also reflect more universal properties in physics. I like to spend time considering unusual device structures and their physical properties. It would be an added pleasure to reveal some important fundamental physics related to these structures.

How and when did you join RIKEN?
I joined in RIKEN as a Special Postdoctoral Researcher in 2019 to continue my experiments on superconductor-semiconductor heterostructures. I made this move partly because my mentor, Seigo Tarucha, an expert in solid-state information processing, moved to RIKEN.

What has been your most memorable experience at RIKEN?
My most memorable experience at RIKEN so far was when I observed what is called a 'nonlocal Josephson effect' (Matsuo, S. *Commun. Phys.* **5**, 221; 2022). This could pave the way to engineering short-range coherent coupling between superconducting qubits.

When I initially looked at the first data, I couldn't believe it. So after finishing the measurement, I carefully checked if the device structure was correctly fabricated using a scanning electron microscope.

For more on Sadashige Matsuo's research go to page 19.

Then I immediately started the fabrication of new devices with the same structure. After I reproduced the original data with the new devices, I finally recognized the importance of the concept.

A Josephson junction is made by sandwiching a thin layer of a non-superconducting material between two layers of superconducting material, so that pairs of superconducting electrons tunnel right through the non-superconducting barrier from one superconductor to another.

We showed that short-range, coherent coupling can occur between two different Josephson junctions. This coupling could be used to transmit information across short distances.

What are your goals?
One of my goals is to build a new conceptual quantum device to answer questions in fundamental physics, such as those around the existence of Majorana fermions, an elementary particle that is its own antiparticle. Another goal is to help make my field of research more active across Japan.

A welcoming presence

Kei Grace Yamada

Human resources staff, International Affairs Division

Tell us about your work at RIKEN.

The international support team (IST) aids international researchers by helping to provide them with the best possible research environment and life in Japan. As part of this, I organize welcome sessions for newcomers, sessions for when they leave RIKEN, and I also assist with language, housing and any family needs.

How did you join RIKEN?

Previously, I worked as a producer on business summit events, but the job wasn't quite right for me. I had heard about RIKEN and I admired the work environment here, so I decided on a change of career.

> *Since RIKEN is very international, I have to look after people who come from very different backgrounds.*

Can you tell us about your background?

I was born and raised in Australia and I came to live in Japan in 2014. I studied Japanese as a second language at high school and majored in Japanese culture, media and history at university. Interestingly, I've never studied or worked in science, but I enjoy supporting other people in pursuing their goals.

What kind of support does RIKEN offer to its non-Japanese staff?

I'm confident in saying that RIKEN provides excellent support for international staff in Japan. The burdens of our researchers' lives are eased by my team, so that they can concentrate on their work in a supportive environment. This includes help with visas, housing, healthcare, childcare, language classes, local government administration, pensions, insurance, social activities and more!

How was the transition to life at RIKEN?

I must say the working environment is exceptional. The administrative staff are always on the job, thinking and caring about their researchers and colleagues. And although Japanese is a second language for me, all signs and announcements at RIKEN are in both Japanese and English, which is rare in Japan. I've never felt that I was missing out on anything.

What is the most challenging aspect of your job?

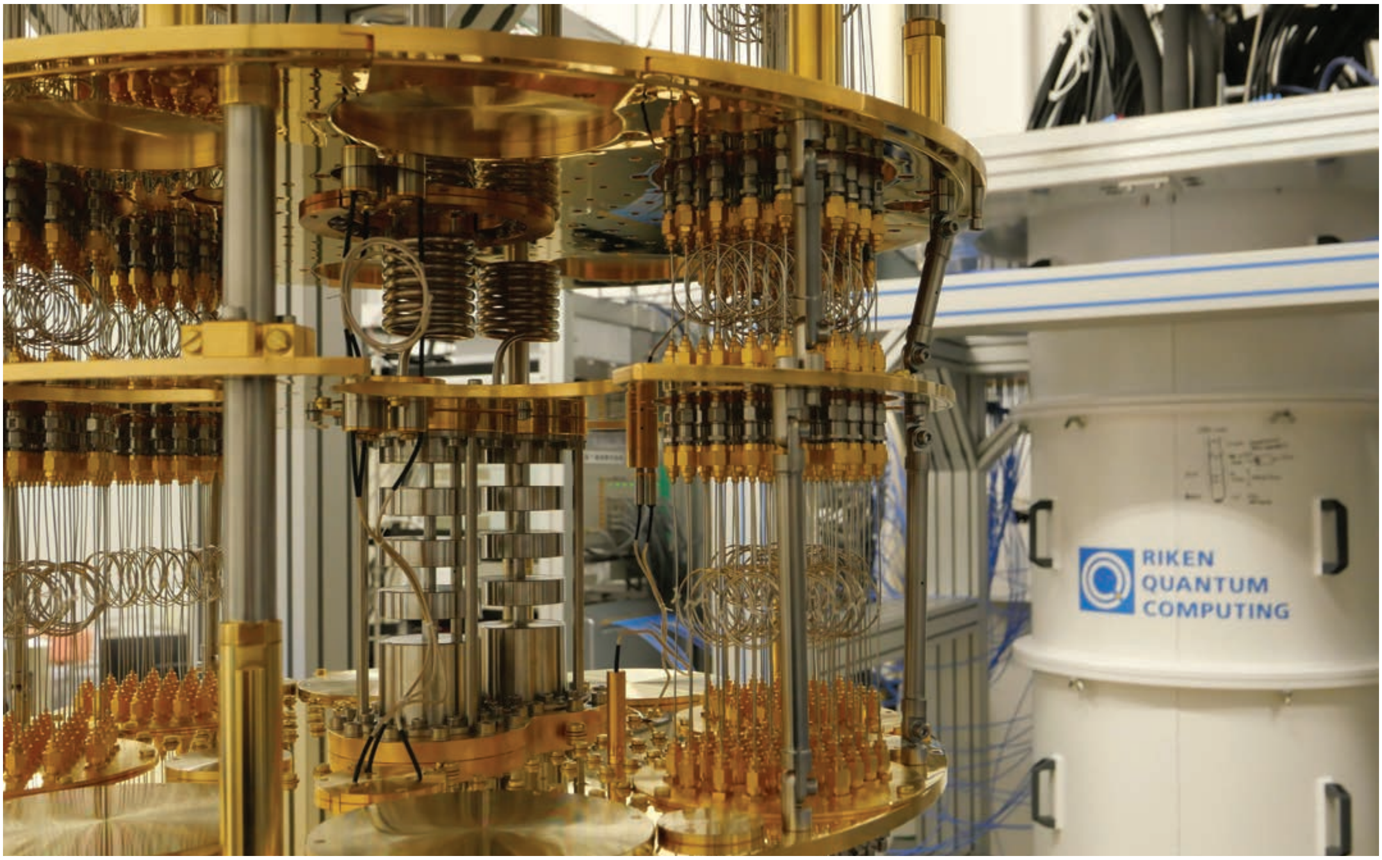
Since RIKEN is very international, I have to look after people who come from very different backgrounds. It's challenging to respond to each of their needs. Each international researcher has different needs, but sometimes I can 'over-support' them because I want them to feel they are part of the community while they are in Japan.

What would you say to people considering joining RIKEN?

Japan is rich in history and culture and I'm sure it will help you enrich your scientific activities directly and indirectly. My team and I are always here to help with daily life at RIKEN and in Japan more broadly. I also hope that they might want to remain in Japan long-term and contribute to solving global issues with our top laboratories. ■

Careers at RIKEN

For further information, visit our Careers page: www.riken.jp/en/careers, or e-mail: pr@riken.jp



Supercomputer Fugaku will be linked to the ‘A’ quantum computer, a 64-qubit machine that is being made accessible to other researchers by RIKEN via the cloud.

Integrating quantum computers and supercomputers

RIKEN is set to run a big, innovative, new quantum-supercomputer hybrid platform in partnership with SoftBank Corp., a multinational investment holding company headquartered in Japan.

Two quantum computers will be connected to the supercomputer Fugaku. First, a 100-qubit superconducting quantum computer developed by IBM, which is headquartered in the United States, will be installed in the same building as Fugaku. After that, a second more than 20-qubit trapped-ion quantum computer will be installed at RIKEN's Wako campus. The quantum computer was developed by Quantinuum, a computing company formed by the merger of the United Kingdom-based Cambridge Quantum and US-based Honeywell Quantum Solutions.

With the support of implementing partners at the University of Tokyo and Osaka University, RIKEN and Softbank will then help develop software to allow the supercomputer to be connected to the quantum computers.

Through this project, RIKEN hopes to advance so-called noisy intermediate-scale quantum computers by connecting them with conventional computers to allow applications development. This will advance quantum computer use in the medium term, until issues with scalability and error correction are resolved.

This is part of a project to enhance post-5G information and communication system infrastructure run by the New Energy and Industrial Technology Development Organization (NEDO), which is part of Japan’s Ministry of Economy, Trade and Industry.

RIKEN has also been developing quantum-classical computer hybrids as part of its Transformative Research Innovation Platform of RIKEN platforms (TRIP) initiative. This links up RIKEN’s cutting-edge platforms—such as its supercomputers, large synchrotron radiation facilities and bioresource projects—to drive a pioneering digital research transformation. As part of the TRIP project, Fugaku will also be connected to the Japanese ‘A’ superconducting quantum computer.

www.riken.jp/en/news_pubs/news/2023/20231122_1/

'Dynamic Resilience' program to aid healthy aging

RIKEN has been awarded major funding from the Dynamic Resilience Program to explore the immune system mechanisms behind centenarian 'dynamic resilience'—or the maintenance of health in aging. The program is run by Wellcome Leap, a non-profit founded by the United Kingdom-based Wellcome Trust, and funding will go towards work done in collaboration with scientists at Keio University and Kyushu University in Japan.

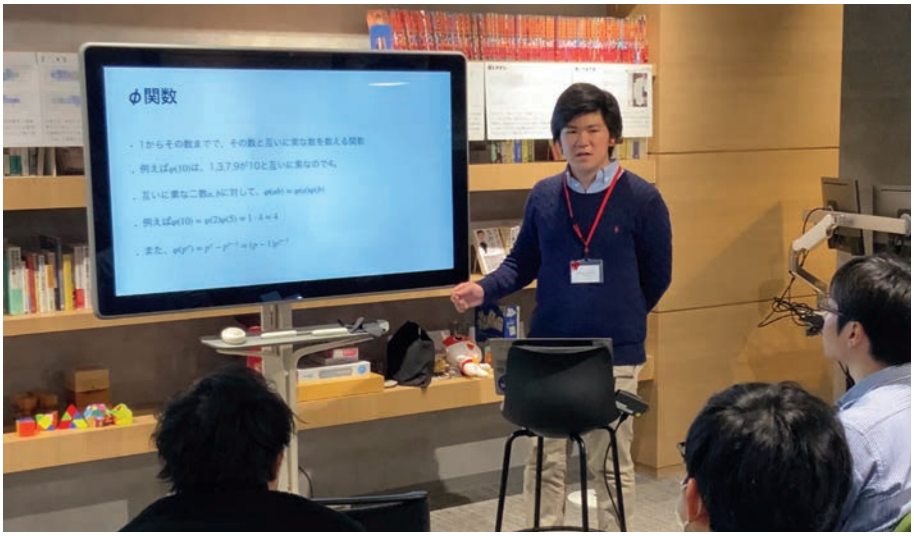
Health resilience is the ability to recover from a damaged or exhausted state after significant stress events, such as infection, injury, surgery, or stroke. In most of these conditions, immune processes in the central nervous system and peripheral systems play important roles in recovery.

"We think it is possible that centenarians have unique immune functions that promote recovery from stress events," says Hiroki Sasaguri of the RIKEN Center for Brain Science, who will lead the group. Centenarians tend to be remarkably healthy, maintaining good health until they reach their late nineties, and thus represent the ultimate phenotype of health resilience, he adds.

Joining him are Kazuyoshi Ishigaki from the RIKEN Center for Integrative Medical Sciences; Takashi Sasaki, Sumihiro Maeda, and Kenya Honda from Keio University; and Takahiro Masuda from Kyushu University. The group will use samples obtained from centenarians and supercentenarians, and will develop relevant animal models. The researchers aim to identify new biomarkers and therapeutic targets to induce better health resilience in response to stress events and achieve healthy aging for everyone.

The Dynamic Resilience Program is aimed at accelerating breakthroughs for global health. It is jointly funded by Wellcome Leap and Temasek Trust, a Singapore-based non-profit that promotes social resilience, progress, and cohesion through evidence-based programs that deliver long-term solutions.

www.riken.jp/en/news_pubs/news/2023/20231228_1/



Members of the Masason Foundation, aged nine to 26, presented on their research in Tokyo.

iTHEMS and young scientists connect

Thirteen members of the Masason Foundation—ranging in age from nine to 26—with interests in areas such as mathematics, quantum physics, biology and artificial intelligence, attended an exchange event with RIKEN in late 2023. The event was run by the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS), who sent 10 researchers to the event, and the Masason Foundation, a public interest incorporated foundation dedicated to providing an environment that enables talented young people to develop their skills. At the event, iTHEMS Deputy Program Director Shigehiro Nagataki gave an overview of iTHEMS, while Taketo Sano, a special postdoctoral researcher at iTHEMS, talked about his work on low-dimensional topology. The youngest Masason Foundation member, at just nine years old, introduced his research results on the Napier constant, an expression that arises in the calculation of compound interest, among other things. He shared his excitement at finding a theorem about sequences that converge to the Napier constant. A 13-year-old foundation member and PhD student specializing in quantum physics presented his research results on quasi-particles called Bose polarons. Bose polarons are understood as impurities in a Bose–Einstein condensate, a state in which atoms or molecules, when cooled to near zero, coalesce into a single quantum mechanical state. Bose–Einstein condensates have attracted attention for their potential applications in quantum simulation technology. The student described current experimental studies and work on a more accurate theoretical description of Bose polarons.

www.riken.jp/en/news_pubs/news/2024/20240121_1/

South Korean minister visits RIKEN

In December 2023, Lee Jong Ho, the South Korean Minister of Science and ICT, met RIKEN President Makoto Gonokami at the Wako Campus to discuss cooperation between RIKEN and the Republic of Korea Government Research Institutes.

The delegation was given a tour of the RIKEN Center for Quantum Computing by director Yasunobu Nakamura. The tour included the 'A' superconducting supercomputer. The delegation was also taken through the RI Beam Factory—a heavy-ion accelerator facility—and other facilities of the RIKEN Nishina Center for Accelerator-Based Science by Nishina Center director Hiroyoshi Sakurai.

www.riken.jp/en/news_pubs/news/2023/20231228_1/

RIKEN's highly cited researchers for 2023

Twenty-five RIKEN researchers appeared on Clarivate's Highly Cited Researchers list released in November, 2023. More than 6,800 researchers from 67 nations and regions were recognized on Clarivate's annual list, which identifies highly-cited researchers based on their publications across the past decade or more.
www.riken.jp/en/news_pubs/news/2023/20231130_3/

CROSS-FIELD

- **Takao Someya,** Chief Scientist, Thin-Film Device Lab, RIKEN Cluster for Pioneering Research; Team Leader, Emergent Soft System Research Team, RIKEN Center for Emergent Matter Science
- **Andrzej Cichocki,** Senior Visiting Scientist, Genetic Technology Research Group, Tensor Learning Team, Center for Advanced Intelligence Project
- **Wataru Suda,** Team Leader, Laboratory for Symbiotic Microbiome Sciences, RIKEN Center for Integrative Medical Sciences
- **Masahira Hattori,** Senior Visiting Scientist, Laboratory for Microbiome Sciences, RIKEN Center for Integrative Medical Sciences
- **Osamu Nureki,** Senior Visiting Scientist, Laboratory for Protein Functional and Structural Biology, RIKEN Center for Biosystems Dynamics Research
- **Takaomi Saido,** Team Leader, Laboratory for Proteolytic Neuroscience. RIKEN Center for Brain Science
- **Takashi Saito,** Visiting Scientist, Laboratory for Proteolytic Neuroscience, RIKEN Center for Brain Science
- **Ryotaro Arita,** Team Leader, First-Principles Materials Science Research Team, RIKEN Center for Emergent Matter Science
- **Yoshihiro Iwasa,** Team Leader, Emergent Device Research Team, RIKEN Center for Emergent Matter Science

IMMUNOLOGY

- **Kenya Honda,** Team Leader, Laboratory for Gut Homeostasis, RIKEN Center for Integrative Medical Sciences
- **Koji Atarashi,** Senior Visiting Scientist, Laboratory for Gut Homeostasi, RIKEN Center for Integrative Medical Sciences

NEUROSCIENCE AND BEHAVIOR

- **Susumu Tonegawa,** RIKEN Fellow, RIKEN

PHYSICS

- **Franco Nori,** Chief Scientist, Theoretical Quantum Physics Laboratory, RIKEN Cluster for Pioneering Research; Team Leader, Quantum Information Physics Theory Research Team, RIKEN Center for Quantum Computing
- **Chihaya Adachi,** Senior Visiting Scientist, Surface and Interface Science Laboratory, RIKEN Cluster for Pioneering Research
- **Yoshinori Tokura,** Director, RIKEN Center for Emergent Matter Science
- **Naoto Nagaosa,** Deputy Director, RIKEN Center for Emergent Matter Science
- **Motohiko Ezawa,** Visiting Scientist, Strong Correlation Theory Research Group, RIKEN Center for Emergent Matter Science

PLANT AND ANIMAL SCIENCE

- **Kazuki Saito,** Director, RIKEN Center for Sustainable Resource Science
- **Kazuo Shinozaki,** RIKEN Honorary Science Advisor, RIKEN; Senior Visiting Scientist, RIKEN Center for Sustainable Resource Science
- **Hitoshi Sakakibara,** Senior Visiting Scientist, Mass Spectrometry and Microscopy Unit, Technology Platform Division, RIKEN Center for Sustainable Resource Science
- **Mitsunori Seo,** Senior Visiting Scientist, Mass Spectrometry and Microscopy Unit, Technology Platform Division, RIKEN Center for Sustainable Resource Science
- **Lam-Son Phan Tran,** Senior Visiting Scientist, Bioproductivity Informatics Research Team, RIKEN Center for Sustainable Resource Science
- **Takayuki Tohge,** Visiting Scientist, Metabolomics Research Group, RIKEN Center for Sustainable Resource Science

MOLECULAR BIOLOGY AND GENETICS

- **Toshiro Sato,** Senior Visiting Scientist, Laboratory for Lung Development and Regeneration, RIKEN Center for Biosystems Dynamics Research

GEOSCIENCE

- **Naoto Yokoya,** Team Leader, Geoinformatics Team, Goal-Oriented Technology Research Group, RIKEN Center for Advanced Intelligence Project

RIKEN and imec sign memorandum

In November, RIKEN and the Interuniversity Microelectronics Centre (IMEC), a hub for nanoelectronics and digital technology that is headquartered in Belgium, signed a Memorandum of Cooperation. The two research institutions pledged to explore collaboration opportunities, and to exchange knowledge through the organization of joint lectures, seminars and symposia.

Through this memorandum, RIKEN hopes to enhance its new initiative, the Transformative Research Innovation Platform of RIKEN platforms (TRIP). This institute-wide cross-disciplinary project aims to link-up RIKEN's cutting-edge research platforms—such as its supercomputers, large synchrotron radiation facilities, bio-resource projects—to drive a pioneering digital transformation of research.

For example, RIKEN is developing the technologies necessary for next-generation semiconductors and is also pioneering the science of prediction in a wide range of fields, including in life sciences, AI and mathematics.

By leveraging its state-of-the-art research and development infrastructure, imec also hopes to contribute to areas ranging from advanced computing and health technologies, to quantum computing, via its leading silicon-based computing platforms.
www.riken.jp/en/news_pubs/news/2023/20231109_2/

OPTOELECTRONICS

Symmetry's importance in the photovoltaic effect

The conversion of light into electricity in special crystals depends on the material's symmetry

A team led by RIKEN researchers has investigated how special crystals convert light into electricity[1]. Their findings will help inform efforts to improve their efficiency, which could lead to the crystals being used in solar cells.

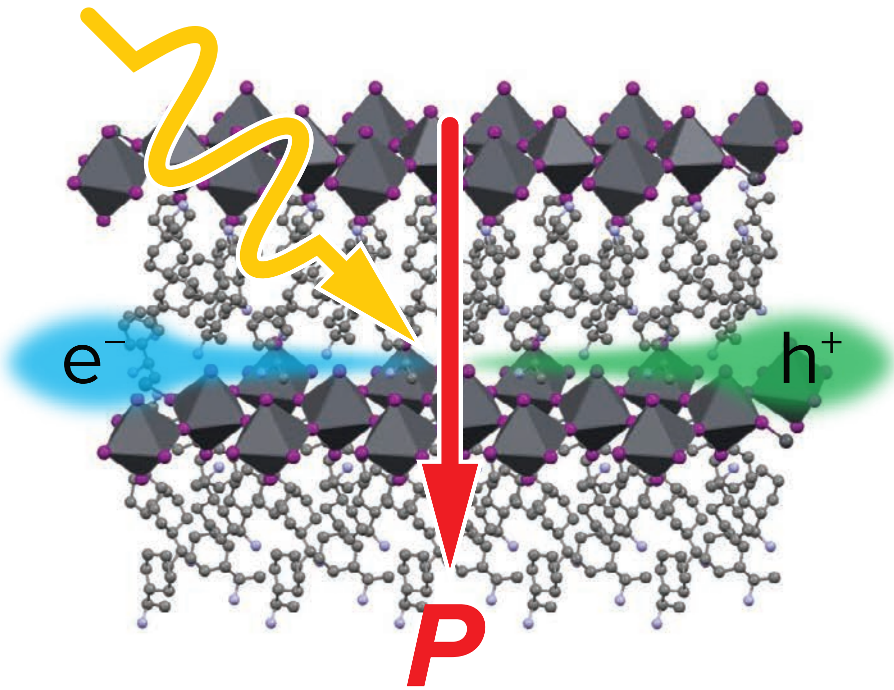
Solar cells convert light into electricity by a phenomenon known as the photovoltaic effect. The vast majority of solar cells consist of two semiconductors wedged together—one with an excess of electrons and the other being electron deficient. This is because the setup has a high conversion efficiency.

But another photovoltaic effect has also been attracting attention—the bulk photovoltaic effect, so called because it only involves a single material. While its conversion efficiency is currently rather low, recent research has suggested ways for improving its efficiency.

There has been much debate about how the bulk photovoltaic effect works. It was originally thought that an electric field generated by polarizations within the material gave rise to the effect, but a new explanation has recently been gaining currency.

In this new mechanism, light shifts the electron clouds in the material and these shifts propagate, generating a current. This current has attractive properties, including an ultrafast response and dissipation-less propagation.

Materials known as organic–inorganic hybrid perovskites (OIHPs) have great potential for making optoelectronic devices.



Schematic illustration of the bulk photovoltaic effect along the non-polar axis of the organic–inorganic hybrid perovskite. The yellow arrow represents of a photon of light, while the blue and green clouds indicate an electron and a 'hole', respectively. The red arrow is the polarization axis.

The bulk photovoltaic effect in OIHPs has generally been ascribed to the old macroscopic polarization mechanism.

"Built-in electric fields in materials have often been considered as the origin of the bulk photovoltaic effect in OIHPs, but without solid evidence," remarks Taishi Noma of the RIKEN Center for Emergent Matter Science.

Now, by studying in detail the bulk photovoltaic effect in OIHP crystals, Noma and his collaborators have found evidence that is consistent with the shift mechanism and rules out the macroscopic polarization mechanism.

Specifically, they observed the bulk photovoltaic effect along a non-polar axis in an OIHP, which cannot be explained in terms of the macroscopic polarization mechanism.

The team's results highlight the importance of the crystal symmetry of the material. The insights gained will help researchers optimize the properties of OIHPs by tailoring their symmetry. In particular, the insights may help improve the efficiency of OIHPs in converting light into electricity.

Noma and his team now intend to explore other kinds of materials. "In principle, shift currents can also be generated in other classes of materials, such as liquid crystals and organic molecular crystals," says Noma. "We would like to extend this study to other materials." ●

Reference

1. Noma, T., Chen, H.-Y., Dhara, B., Sotome, M., Nomoto, T., Arita, R., Nakamura, M. & Miyajima, D. Bulk photovoltaic effect along the nonpolar axis in organic-inorganic hybrid perovskites. *Angewandte Chemie* **62,** e202309055 (2023).

ALLERGIES

Gut bacteria behind better responses to milk-allergy treatment

Children with *Bifidobacteriaceae* bacteria in their guts are more likely to have long-lasting success with immunotherapy for milk allergy

Probiotic supplements might help to boost the typically low success rates of oral immunotherapy for milk allergy, a link between gut bacteria and successful immunotherapy discovered by RIKEN researchers suggests[1].

Children often have allergic reactions to proteins found in cow's milk. Although many grow out of it, for some it becomes a lifelong challenge to avoid all foods that contain milk products, especially when the allergic reactions are severe and include anaphylactic shock.

Oral immunotherapy in the form of a food challenge can reduce the body's allergic response, but in most cases, milk tolerance doesn't last—going a few days without drinking milk causes tolerance to revert to zero, and the whole process, which takes almost a year, must be started all over again.

Those with sustained unresponsiveness tended to have *Bifidobacteriaceae* bacteria in their guts.

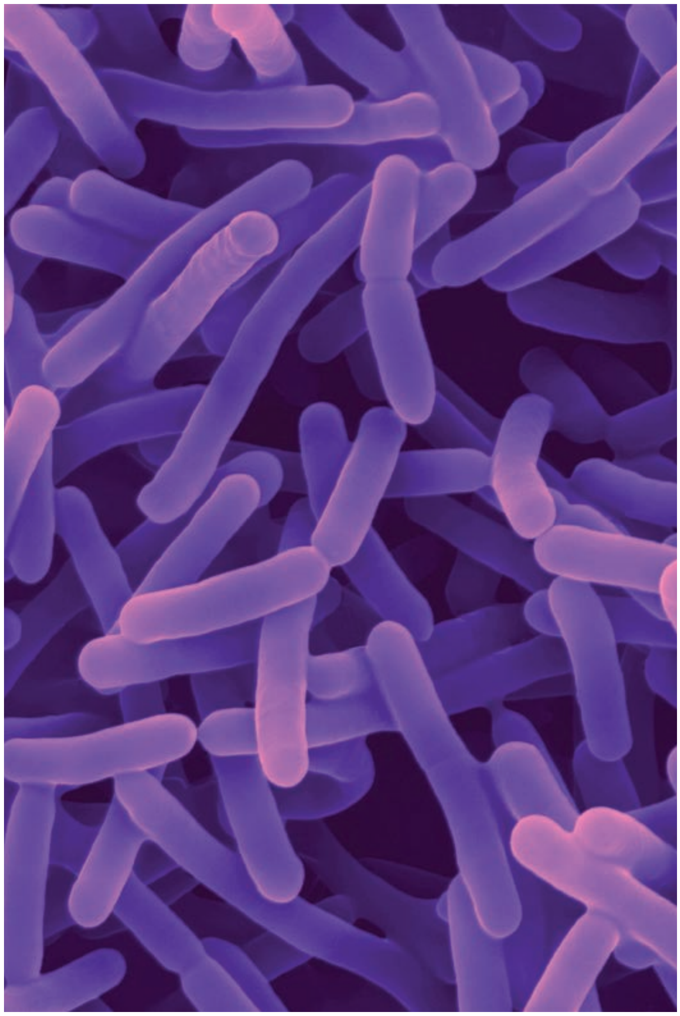
A team led by Hiroshi Ohno of the RIKEN Center for Integrative Medical Sciences suspected that successful treatment, termed sustained unresponsiveness, is related to the type of bacteria, or microbiota, in the gut.

To test this, they examined 29 children with cow's milk allergy who participated in a 13-month milk challenge. Children with milk allergies were initially given a tiny bit of milk, which was gradually increased each day until they had an allergic reaction or until they could drink 44 milliliters of milk without a reaction.

During the study, the researchers measured immunological factors and gut microbiota at several time points. At the end of the 13-month treatment, about 72% of the children could drink the 44 milliliters of milk without any allergic reactions, which was accompanied with improved immunological parameters.

The children then went two weeks without consuming any dairy products, and were tested on the milk challenge again to see whether they could still tolerate milk. As expected, only 25% could tolerate milk after the two-week avoidance period.

The researchers compared the gut microbiota between children who did or did not remain milk tolerant and found that those with sustained unresponsiveness tended to have more *Bifidobacteriaceae* bacteria in their guts.



Colored scanning electron micrograph of *Bifidobacteriaceae* bacteria. Children with such bacteria in their guts are more likely to have long-lasting success with immunotherapy for milk allergy.

"Not only were *Bifidobacteriaceae* bacteria associated with success, but also only children who achieved sustained unresponsiveness exhibited an increase in these bacteria over the course of treatment," says Ohno.

"We have identified gut environmental factors that help establish immune tolerance of a food allergy via oral immunotherapy," says Ohno. "The next step is to examine in more detail the changes in these factors that result from oral immunotherapy for milk allergy and to test the efficacy of the predicted probiotics in increasing the chances of long-term successful immunotherapy." ●

Reference

1. Shibata, R., Itoh, N., Nakanishi, Y., Kato, T., Suda, W., Nagao, M., J-OIT group, Iwata, T., Yoshida, H., Hattori, M. *et al.* Gut microbiota and fecal metabolites in sustained unresponsiveness by oral immunotherapy in school-age children with cow's milk allergy. *Allergology International* **73,** 126–136 (2024).

QUANTUM FLUIDS

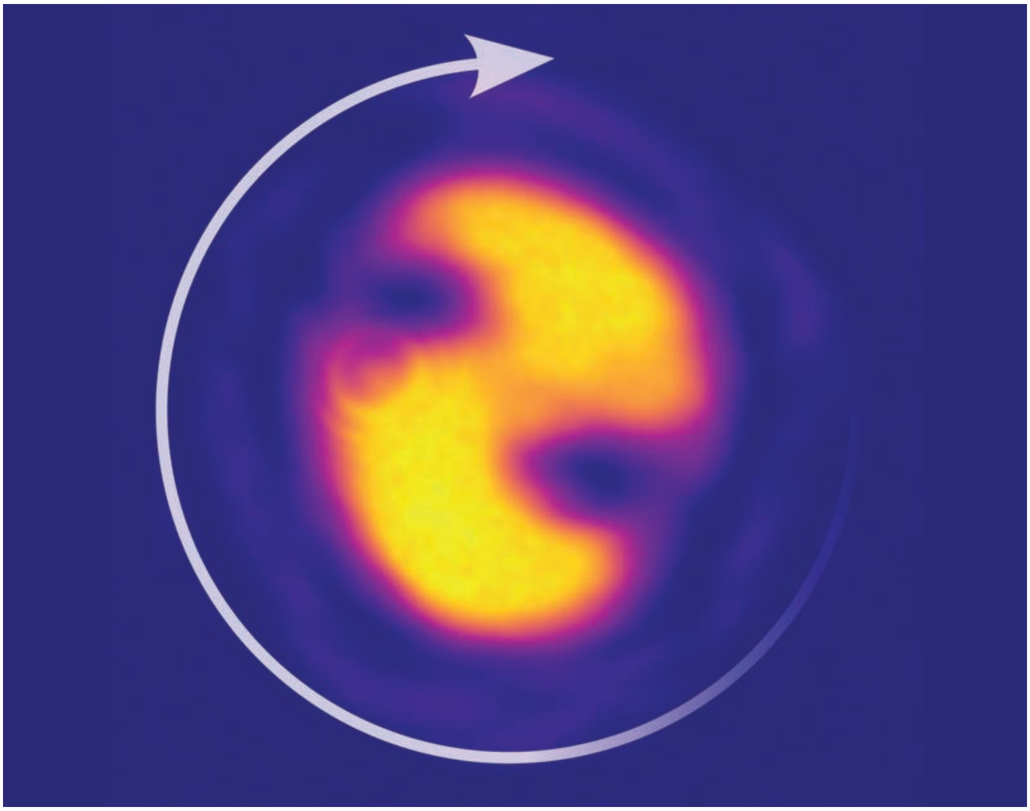
Stirring a quantum system using light

Vortices can be created at will in a superfluid made of light

By using a special combination of laser beams as a very fast stirrer, RIKEN physicists have created multiple vortices in a quantum photonic system and tracked their evolution[1]. This system could be used to explore exotic new physics related to the emergence of quantum states from vortex matter.

In principle, if you were to swim in a pool filled with a superfluid, a single stroke would be all you need to swim an infinite number of laps. That's because, unlike normal fluids like water, superfluids have no resistance to motion below a certain velocity.

Superfluids also behave weirdly when stirred. "If you stir a bucket of water, you typically get just one big vortex," explains Michael Fraser of the RIKEN Center for Emergent Matter Science. "But when you rotate a superfluid, you initially create one vortex. And when you rotate it faster, you get progressively more and more vortices of precisely the same size."



A snapshot of a laser beam that RIKEN researchers used to rapidly stir a polariton condensate. The profile can rotate in a clockwise (indicated) or counter-clockwise direction.

While also seen in liquid helium and atomic systems, a form of superfluidity is displayed by a system made up of particle-like entities known as polaritons, in which a photon of light couples strongly with a negative electron bound to a positive hole in a semiconductor. Researchers want to 'stir' such systems, but this is challenging since it requires using extremely high frequencies—millions of times faster than those needed for atomic systems.

Now, Fraser and co-workers have used a specially crafted laser beam to incoherently stir such a polariton condensate, creating ensembles of vortices.

"These condensates have been around for more than 15 years, and a lot of interesting physics has been done with them," says Fraser. "But rotation of a polariton superfluid causing multiple vortices to collect and freely evolve had not been achieved before."

The team created their special laser beam stirrer by combining a regular laser beam with one that had a donut-like shape (see image). The frequencies of the two beams were slightly off, and this frequency difference matched the frequency needed to rotate polaritons. Using this beam, the researchers could control their speed and direction of rotation, and create vortices at will. They even showed that the faster the rotation, the more vortices could be captured close to the rotation axis.

Furthermore, the experimental measurements they obtained agreed well with simulations based on theory.

"Our rotation scheme thus allows the study of self-ordering vortex dynamics in an open-dissipative platform—one that continually loses and gains particles," explains Fraser. "This is especially exciting as not only do we expect it to exhibit new vortex phenomena, but it also opens up opportunities to study highly quantum, topological phases of light." ●

Reference

1. Redondo, Y. d. V.-I., Schneider, C., Klembt, S., Höfling, S., Tarucha, S. & Fraser, M. D. Optically driven rotation of exciton–polariton condensates. *Nano Letters* **23,** 4564–4571 (2023).

CONFIDENCE BIAS

Artificial intelligence shares our confidence bias

Like humans, AI displays some puzzling dissociations between decisions and confidence

In experiments, an artificial-intelligence model was able to distinguish noisy images of numbers in a similar way that humans do.

The pronounced positive confidence bias that is a characteristic and apparently irrational trait of human decision making has been replicated and dissected using an artificial intelligence (AI) model[1]. The unnerving result by a RIKEN-led team reveals that our inflated sense of confidence might stem from subtle observational cues.

When we glimpse something familiar, we're often able to instantly and confidently conclude a match to that familiar object, even if the balance of evidence doesn't support such a high level of confidence. This dissociation between decision making and confidence level has long perplexed researchers, as it suggests that while we are capable of highly rational decision making, our sense of confidence about our decisions can be quite irrational.

"There's been a tension between theory, which bluntly assumes that humans are rational, and the empirical data, which clearly shows that this is not always the case,"

Surprisingly, the AI models showed exactly the same confidence biases as humans.

notes Hakwan Lau of the RIKEN Center for Brain Science.

This generally occurs when the image is unclear, or noisy. Mathematically, the noisiness of an image can be calculated from its deviation from the clear image by a metric called the signal-to-noise ratio.

But this is where things start to get weird. "If I make an image both more salient and more noisy, but keep the overall signal-to-noise ratio the same, we somehow become more confident in believing we know what we're seeing, even though we aren't seeing any better," says Lau. "It turns out that the structure of the noise, which is usually assumed to be random, actually matters a lot."

Now, Lau and co-workers have investigated the effect of different types of noise on decision confidence using an AI model that specifically reported on confidence.

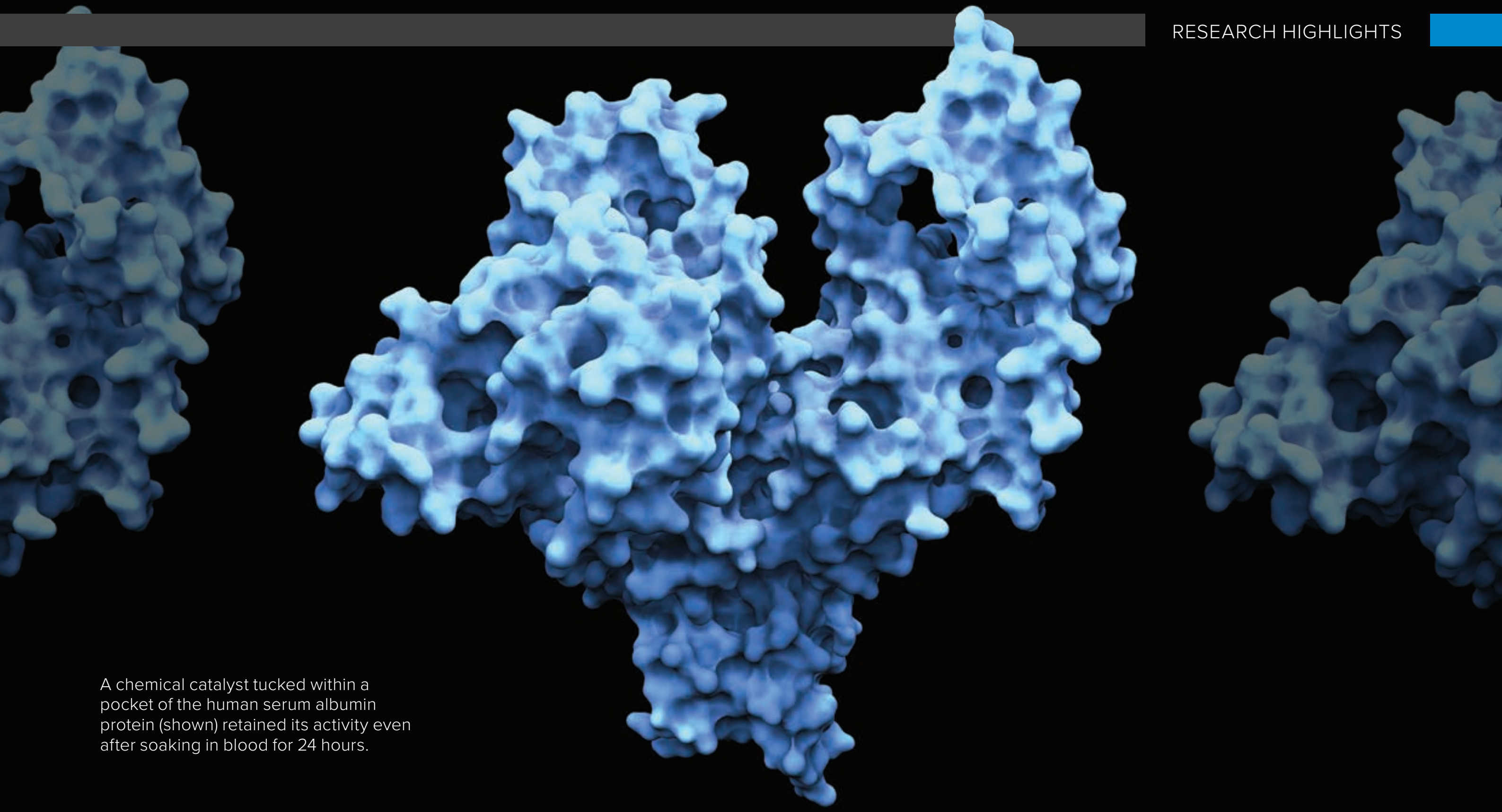
"One always wonders what an AI model is doing," says Lau. "But the great thing with an AI model is that once it learns, unlike with the human brain, we can 'dissect' the model to understand it better."

Surprisingly, the AI models showed precisely the same confidence biases as humans. This seems to be exactly what it is supposed to do, as Lau points out.

"The model is rational in a sense that it learns from the noise structure of natural images, which is different from the standard noise type assumed in signal-processing models," says Lau. "It's the learning of the statistical properties of natural images that lead these models—and presumably our brains too—to have these apparent biases." ●

Reference

1. Webb, T. W., Miyoshi, K., So, T. Y., Rajananda, S. & Lau, H. Natural statistics support a rational account of confidence biases. *Nature Communications* **14**, 3992 (2023).



A chemical catalyst tucked within a pocket of the human serum albumin protein (shown) retained its activity even after soaking in blood for 24 hours.

BIOCATALYSIS

Making medicines inside the body

A robust biocompatible catalyst that is active in blood could lead to safer treatments with minimal side effects

A highly active catalyst capable of synthesizing drug molecules within the body has been developed by RIKEN chemists[1]. In mice, an anticancer drug assembled near tumors using the injected catalyst suppressed tumor growth.

In conventional medicines delivered by injection or pill, the active drug molecule circulates throughout the body, flooding not only the target site but also healthy tissues. The resulting side effects can be so serious that they can cause permanent damage and force treatment to be stopped.

Assembling drug molecules at target sites within the body could make them more effective while minimizing their side effects.

"The direct synthesis of drugs in the body would enable drugs to treat diseases without causing side effects in healthy tissues," says Katsunori Tanaka, chief scientist of the RIKEN Biofunctional Synthetic Chemistry Laboratory. "That's why we need a biocompatible biocatalysis system to perform drug synthesis near target sites in the body."

The team targeted drug assembly in the body using a catalytic chemical reaction called olefin metathesis. "Olefin metathesis is one of the most efficient methods for constructing carbon–carbon double bonds for synthesizing drugs," explains Tanaka. "If it could be worked out in the body, it should enable us to synthesize many different types of drugs."

Most chemical catalysts are rapidly deactivated by biomolecules in the bloodstream. To overcome this problem, the team wrapped a ruthenium-based olefin metathesis catalyst inside a protective protein called human serum albumin (see image).

Tanaka's team had previously shown that a ruthenium chloride complex embedded inside human serum albumin—forming a catalytic assembly called an artificial metalloenzyme—was somewhat active in blood[2]. Now, they have shown that switching to a ruthenium iodide complex produces a far superior artificial metalloenzyme.

At low catalyst concentrations, the new albumin-based ruthenium iodide (AlbRuI) catalyst catalyzed three types of olefin metathesis reactions in blood at high yield.

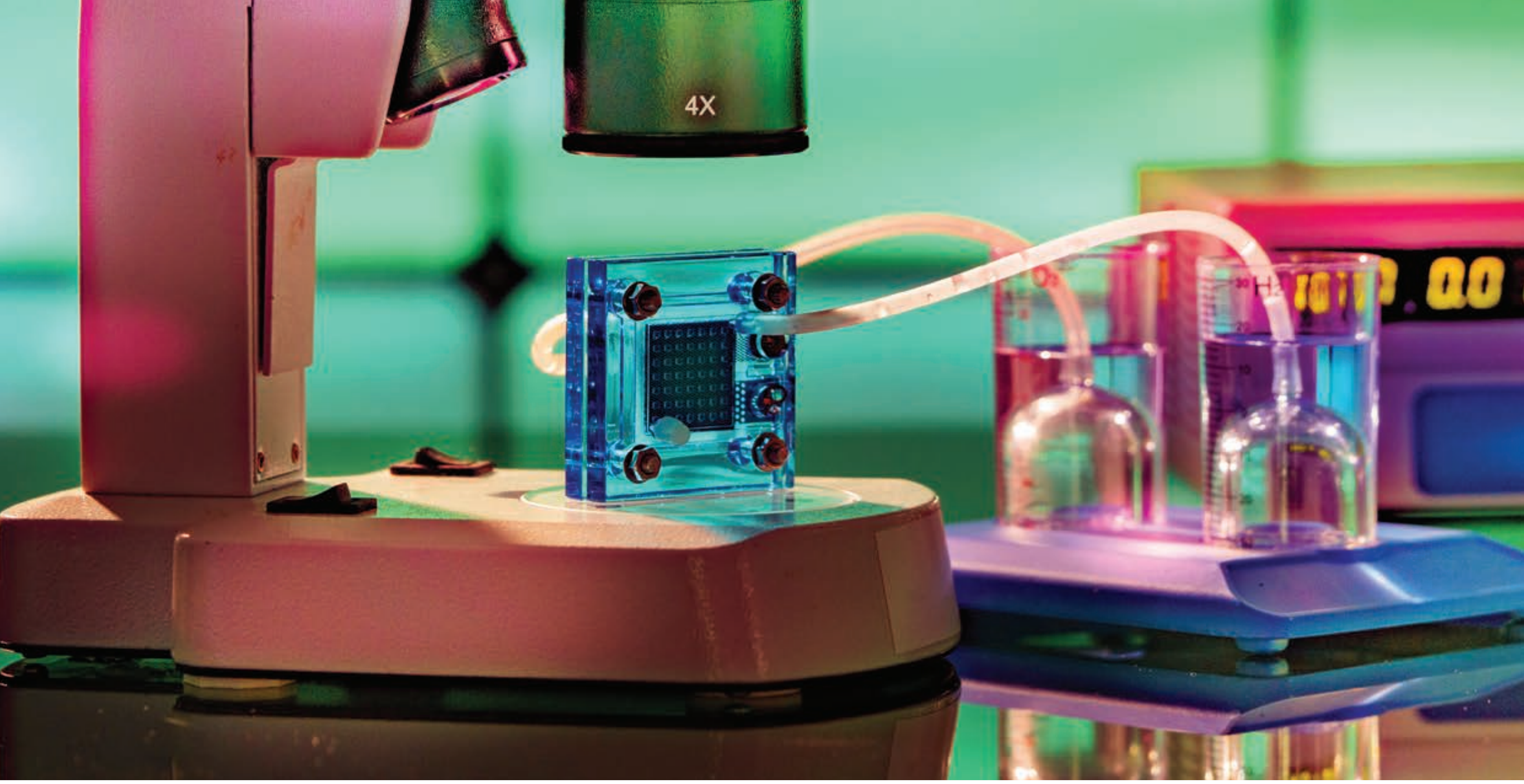
"AlbRuI also showed robust stability for 24 hours in blood," says Tanaka. "This expands the biocompatibility of artificial metalloenzymes and opens the door for developing general, metal-based artificial metalloenzymes for catalytic reactions in blood."

The team also showed that a low dose of cancer-targeting AlbRuI significantly inhibited tumor growth in mice through localized synthesis of an antitumor drug.

The team intends to expand the use of their catalyst. "We hope to use AlbRuI to synthesize a variety of bioactive molecules," says Tanaka. "Then we could use it to treat not only cancer but also other diseases without side effects."

References

1. Nasibullin, I., Yoshioka, H., Mukaimine, A., Nakamura, A., Kusakari, Y., Chang, T. C. & Tanaka, K. Catalytic olefin metathesis in blood. *Chemical Science* **14,** 11033–11039 (2023).
2. Nasibullin, I., Smirnov, I., Ahmadi, P., Vong, K., Kurbangalieva, A. & Tanaka, K. Synthetic prodrug design enables biocatalytic activation in mice to elicit tumor growth suppression. *Nature Communications* **13,** 39 (2022).



A solid electrolyte that is capable of transporting hydride ions at room temperature could improve hydrogen fuel cells (pictured) used in cars and other applications.

HYDROGEN ENERGY

New membrane material brings hydrogen economy closer

Hydrogen batteries and fuel cells could be more viable now that a long-standing problem with membranes has been overcome

In an advance that promises to bring the advantages of hydrogen batteries and fuel cells within practical reach, RIKEN researchers have developed a solid electrolyte for transporting hydride ions at room temperature[1].

Hydrogen is the ultimate green fuel, producing only water when burnt. But for hydrogen energy to become widespread, hydrogen fuel cells and batteries need to be simple, safe and efficient.

Hydrogen fuel cells currently used in electric cars generate energy by protons passing from one end of the fuel cell to the other through a polymer membrane. This membrane must be continually hydrated to ensure efficient and rapid proton movement. This necessity increases the complexity and cost of batteries and fuel cells, which limits the feasibility of a hydrogen economy.

Scientists have been striving to overcome this problem, but they have been struggling to find a way to conduct negative hydride ions through solid materials, particularly at room temperature.

The wait is now over. "We have achieved a true milestone," says Genki Kobayashi at the RIKEN Cluster for Pioneering Research. "Our result is the first demonstration of a hydride-ion-conducting solid electrolyte at room temperature."

The team had been experimenting with lanthanum hydrides because they have a crystal structure, can capture and release hydrogen relatively easily, have a very high hydride-ion conduction, and work below 100 degrees Celsius.

But at room temperature, the number of hydrogen atoms attached to lanthanum fluctuates between two and three, which is too few for efficient conduction. This was the biggest obstacle overcome in the new study.

The researchers obtained the results they were hoping for by replacing some of the lanthanum with strontium and adding a pinch of oxygen.

The team found that crystalline samples of the material could conduct hydride ions at a high rate at room temperature. They tested their performance in a solid-state fuel cell made from the new material and titanium, varying the amounts of strontium and oxygen in the formula. With the optimal amount of strontium, the team observed complete conversion of titanium into titanium hydride, indicating that virtually no hydride ions had been wasted.

"In the short term, our results provide material design guidelines for hydride ion-conducting solid electrolytes," says Kobayashi. "In the long term, we believe this is an inflection point in the development of batteries, fuel cells and electrolytic cells that operate by using hydrogen."

The next step is to improve performance and create electrode materials that can reversibly absorb and release hydrogen. This would allow batteries to be recharged and make it possible to place hydrogen in storage and release it easily when needed. ●

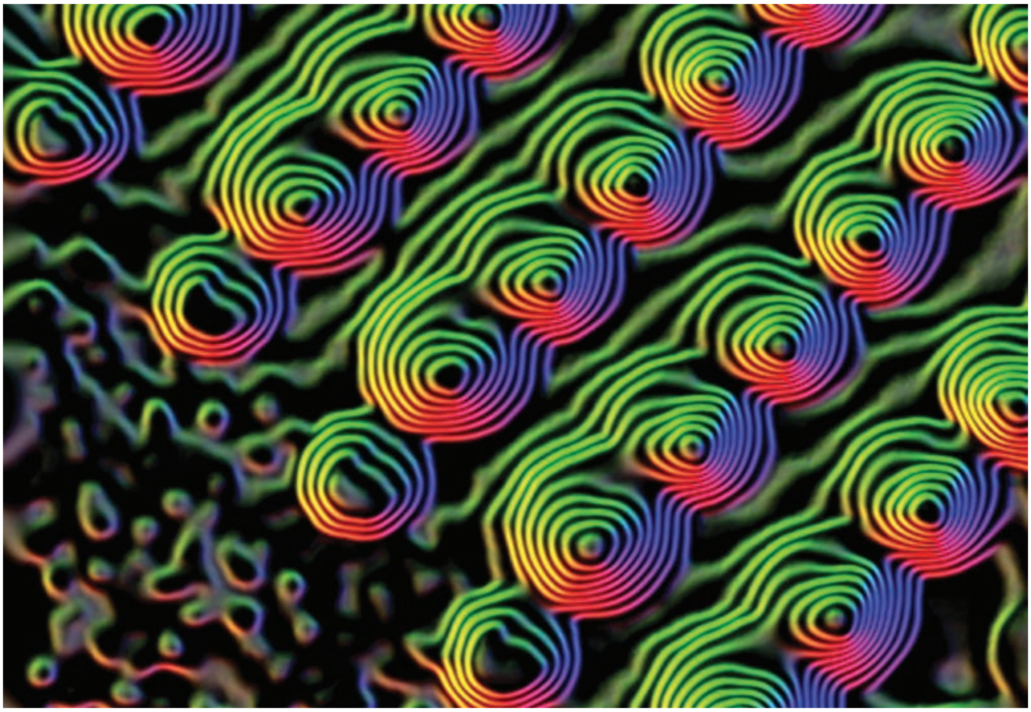
Reference

1. Izumi, Y., Takeiri, F., Okamoto, K., Saito, T., Kamiyama, T., Kuwabara, A. & Kobayashi, G. Electropositive metal doping into lanthanum hydride for H^- conducting solid electrolyte use at room temperature. *Advanced Energy Materials* **13,** 2301993 (2023).

SKYRMIONS

Scrutinizing skyrmions to serve spintronics

Neutron-scattering experiments confirm the dynamics of magnetic whirlpools



Materials that give rise to helical patterns of magnetic flux, called skyrmions, are promising for ultralow-energy devices.

RIKEN researchers have brought low-energy devices based on spintronics one step closer, by measuring the dynamics of tiny magnetic vortices[1].

At present, all our information technologies are based on conventional electronics, which involves shunting electric charge around circuits. However, electrons have another property known as spin, which could be exploited to make faster and more efficient devices.

Hazuki Kawano-Furukawa of the RIKEN Center for Emergent Matter Science and her co-workers are leading efforts to develop this field of spintronics. In particular, they are exploring the use of nanoscale magnetic whirlpools called skyrmions.

"Skyrmions can be controlled with significantly smaller currents or electric fields," explains Kawano-Furukawa. "This makes them highly promising for future applications in information and communication technologies, such as computer memory that doesn't need power to keep stored data."

The team focused on the material manganese monosilicide—a helimagnet, so-called because the spins in its molecular lattice align in helical patterns. Extremely sensitive equipment was necessary to measure the lowest energy magnetic excitations in the skyrmion states.

"The only method that fulfills both the spatial and energy resolution requirements for this purpose is the neutron spin echo technique," says Kawano-Furukawa. "We conducted experiments using the state-of-the-art IN15 neutron spin echo spectrometer at the Institut-Laue-Langevin in Grenoble, France. This instrument boasts the highest performance in the world for studying the dynamics of materials in magnetic fields."

The spin echo method works by illuminating a sample with a beam of neutrons, and measuring how the sample's magnetic fields affect the spin and velocity of the neutrons.

Through their observations, the team verified theoretical predictions that the string-like structures of skyrmions (see image) cause an asymmetric dispersion of excitations in the lattice of manganese monosilicide. In Kawano-Furukawa's words, these excitations 'know' if they are traveling parallel or antiparallel to the cores of the skyrmion whirlpools. This confirmation of theory opens up the way to better exploit skyrmions.

The team had to wait two years to confirm their results. "We conducted our initial experiment in October 2018," she says. "However, to draw final conclusions, we needed to confirm that the behavior was observed only in the skyrmion phase, and not in another magnetic structure called the conical phase. Due to the COVID-19 pandemic, the follow-up experiment was postponed to January 2021 and was carried out remotely, posing various challenges."

The team now intends to conduct further research on how magnetic skyrmions are generated. "We aim to investigate the coexistence of the conical and skyrmion phases in manganese monosilicide," says Kawano-Furukawa. ●

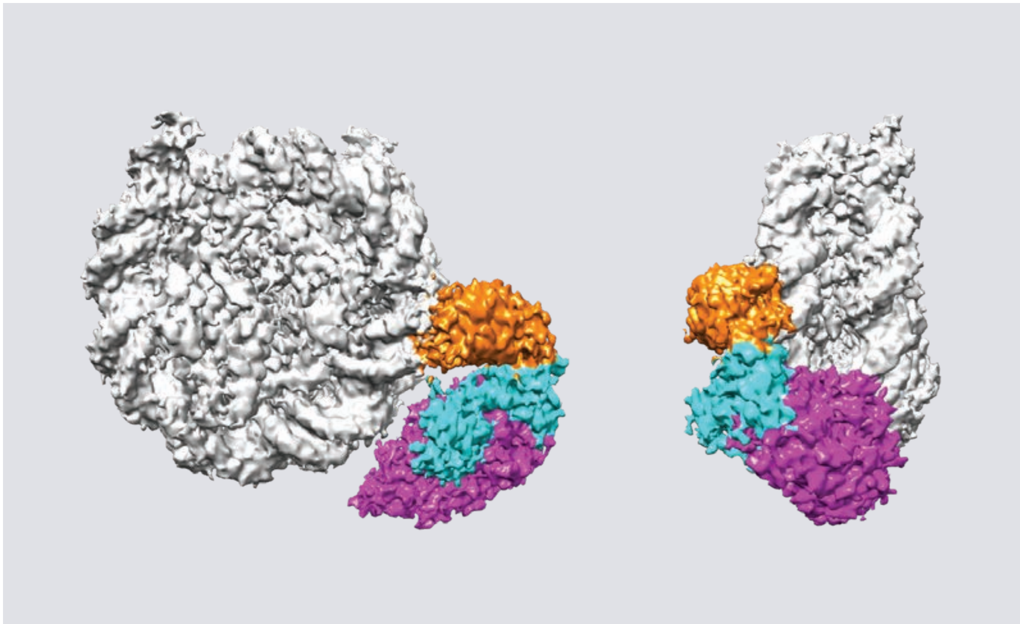
Reference

1. Soda, M., Forgan, E. M., Blackburn, E., Campillo, E., Ryukhtin, V., Hoffmann, I., Kikkawa, A., Taguchi, Y., Yoshizawa, H. & Kawano-Furukawa, H. Asymmetric slow dynamics of the skyrmion lattice in MnSi. *Nature Physics* **19,** 1476–1481 (2023).

EPIGENETICS

Cellular read–write mechanisms for gene expression revealed

Researchers have uncovered how instructions for gene expression are relayed



Two views of how p300/CBP (colored) propagates acetylation of histones in the nucleosome complex (gray). The orange 'read' domain recognizes and binds to acetylations on H3–H4, while the magenta 'write' domain transcribes acetylations from H3–H4 to H2B–H2A.

The 'read–write' mechanism by which cells replicate and use chemical instructions for expressing genes has been uncovered by RIKEN researchers[1].

The quality and quantity of gene expression correlates not only with instructions by transcription factors but also with chemical modifications to the various histone proteins, which provide a scaffold for DNA in the chromosomes.

Scientists have long argued whether these modifications to histones are the epigenetic cause for activating gene expression. And, if that is the case, how they activate gene expression and are maintained during the process of mitosis, in which a cell divides into two daughter cells.

"Whether histone modifications are the epigenetic cause for gene expression has remained a hypothesis because no one had ever seen whether histone modifications self-replicate," explains Takashi Umehara of the RIKEN Center for Biosystems Dynamics Research.

To explore this question, Umehara and his team focused on a protein known as p300/CBP—an enzyme that can both introduce and bind to acetyl-group modifications (acetylations) on histone proteins. In particular, the researchers were interested in specific acetylations on the histone H3–H4 complex to which p300/CBP binds. These acetylations are known to activate gene expression in nearby DNA sequences.

But H3–H4 is just one component of a larger 'nucleosome' assembly, which also includes the histone H2B–H2A complex. All of these various histones can carry distinct acetylation patterns, and the causal relationships between their acetylations have not been well understood.

Now, Umehara and colleagues have developed an experimental technology that allowed them to generate histones with acetylations at defined sites. They then monitored how p300/CBP interacts with and acetylates a nucleosome containing these selectively acetylated human histones.

The team found that p300/CBP recognizes and binds to specific acetylation marks on the H3–H4 complex. The enzyme then replicates acetylation marks to unacetylated sites of H3–H4, while also transcribing them from H3–H4 to H2B–H2A within the same nucleosome. Since this newly acetylated H2B–H2A complex is more likely to be stripped from the nucleosome, a model emerges in which it finally instructs which genes to be transcribed by the cellular transcription machinery.

These results provide an unprecedented glimpse into how p300/CBP inherits acetylation marks to newly divided cells and utilizes those marks epigenetically for gene expression. "I could never have imagined such an elegant yin–yang mechanism for the inheritance and expression of epigenetic information," says Umehara.

Umehara's team now aims to explore how well conserved these processes are across non-animal species, including yeast and plants. ●

Reference

1. Kikuchi, M., Morita, S., Wakamori, M., Sato, S., Uchikubo-Kamo, T., Suzuki, T., Dohmae, N., Shirouzu, M. & Umehara, T. Epigenetic mechanisms to propagate histone acetylation by p300/CBP. *Nature Communications* **14**, 4103 (2023).

Upon maturation, horsehair worms manipulate host mantises into entering water, where the parasites then reproduce.

PARASITIC MANIPULATION

Stolen genes enable parasites to control host behavior

Genes acquired from mantises allow horsehair worms to manipulate their hosts, causing them to leap into water

Parasitic horsehair worms manipulate their hosts using genes they have snatched from their hosts, RIKEN biologists have discovered[1]. This could open new avenues of research into how gene transfer occurs between multicellular eukaryotes.

Like many parasites, horsehair worms manipulate their host's behavior. Born in water, they use aquatic insects to hitchhike to dry land, where they are eaten by terrestrial insects such as mantises. On entering a host, a horsehair worm starts growing and manipulating the host's behavior. The mature horsehair worm induces the host to jump into water, often to the host's demise, so it can complete its life cycle by reproducing.

Previous research suggests that horsehair worms hijack their hosts' biological pathways and increase movement toward light, which causes the hosts to approach water. Scientists believe this involves molecules mimicking those of the hosts' central nervous systems. But how parasites developed this kind of molecular mimicry has remained a mystery.

To explore this, a team led by Tappei Mishina at the RIKEN Center for Biosystems Dynamics Research analyzed whole-body gene expression in a horsehair worm before, during, and after manipulating its mantis host.

They found more than 3,000 hairworm genes were expressed more when hosts were being manipulated, and 1,500 hairworm genes were expressed less. In contrast, gene expression in the mantis brain did not change. This suggests that horsehair worms manipulate their hosts' nervous systems by producing their own proteins.

To explore the origins of the genes that horsehair worms use to manipulate mantises, the researchers searched a protein database. "Strikingly, many of the horsehair worm genes that could play important roles in manipulating their hosts were very similar to mantid genes, suggesting that they were acquired through horizontal gene transfer," says Mishina. Horizontal gene transfer involves the transfer of genes between organisms, but not through reproduction.

Further analysis supported this hypothesis: more than 1,400 horsehair worm genes matched those in mantises, but were lacking or differed greatly from those of horsehair worm species that do not use mantis hosts.

The many mimicry genes the team identified are likely the result of multiple horizontal gene-transfer events from various mantid species during the hairworms' evolution. These genes—particularly those associated with neuromodulation, attraction to light, and circadian rhythms—appear to play a role in host manipulation.

Horizontal gene transfer is also a major way that bacteria evolve resistance to antibiotics. By finding more examples of horizontal gene transfer, we will gain insight into this phenomenon and evolution in general, Mishina believes. "The many cases of horizontal gene transfer that we have found in the hairworm can be a good model for study," he says. ●

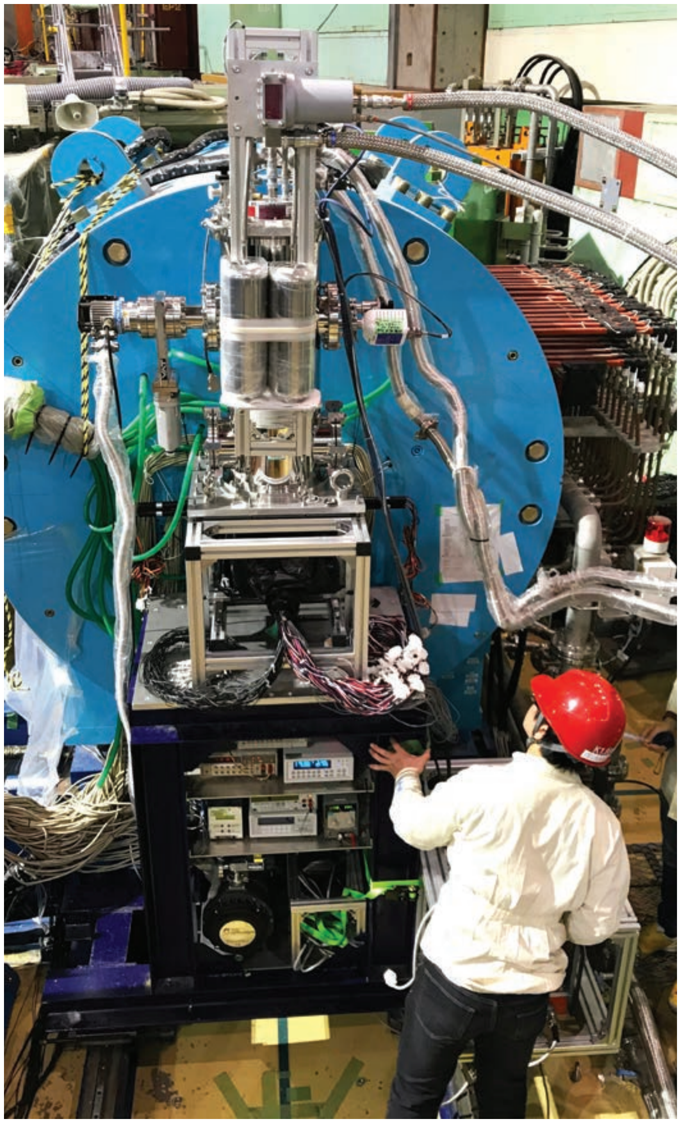
Reference

1. Mishina, T., Chiu, M.-C., Hashiguchi, Y., Oishi, S., Sasaki, A., Okada, R., Uchiyama, H., Sasaki, T., Sakura, M., Takeshima, H. *et al.* Massive horizontal gene transfer and the evolution of nematomorph-driven behavioral manipulation of mantids. *Current Biology* **33,** 4988–4994 (2023).

HYPERNUCLEAR PHYSICS

Measuring the lifetimes of strange nuclei

The lifetimes of nuclei with a property known as strangeness have been precisely determined



A researcher working on the main detector used in their experiment. It is housed in the Hadron Hall at the J-PARC proton accelerator facility.

RIKEN physicists have shown how hypernuclei—nuclei that contain exotic subatomic particles besides the protons and neutrons that make up normal atomic nuclei—can be generated and characterized[1]. This promises to extend our understanding of the fundamental nature of matter.

Quarks are the building blocks of matter. The standard model of elementary particles includes six of them with different flavors—up, down, charm, strange, top and bottom—along with their antiparticle equivalents.

The proton contains two up quarks and one down quark, while the neutron consists of one up quark and two down quarks.

“This breakthrough has opened new avenues in the field of hypernuclear physics.”

However, other three-quark particles can be created by high-energy particle accelerators. For example, a hyperon has at least one strange quark combined with up and down quarks.

“Studying the interactions of hyperons with protons and neutrons advances our understanding of fundamental quark behavior and the strong nuclear force that binds them all together,” explains Yue Ma of the RIKEN Nishina Center for Accelerator-Based Science. “The study of hypernuclei is also valuable for exploring exotic forms of matter and understanding extreme environments in the Universe, such as in neutron stars.”

Working with an international team, Ma and his colleague Fuminori Sakuma have now demonstrated an innovative technique for producing hypernuclei through a process previously thought impossible.

At the J-PARC proton accelerator facility in Ibaraki prefecture, a beam of so-called kaons—a strange quark and an up antiquark—was collided with protons in helium nuclei.

They showed that the kaon could swap its strange quark with an up quark in the proton. This created a neutral subatomic particle called a pion and a so-called Λ-hyperon, consisting of up, down and strange quarks. The Λ-hyperon could then join with what was left of the helium nucleus, creating a hypernucleus made of a proton, two neutrons and the hyperon.

The team measured how long this exotic hypernucleus lived before it decayed, emitting a negatively charged pion in the process. But selecting this pion from all the others was not easy, and it required devising a new method.

“We’ve demonstrated for the first time that, by leveraging a relativistic effect known as the Lorentz boost, we can efficiently select the neutral pion and use it to identify Λ-hyperon production,” says Sakuma. “This breakthrough has opened new avenues in the field of hypernuclear physics.”

The team now aims to investigate another hypernucleus, the hypertriton: one proton, one neutron and one hyperon. Conflicting reports exist about the hypertriton’s lifetime, and the researchers hope their method will help to finally solve this puzzle. ●

Reference

1. Akaishi, T., Asano, H., Chen, X., Clozza, A., Curceanu, C., Del Grande, R., Guaraldo, C., Han, C., Hashimoto, T., Iliescu, M. *et al.* Precise lifetime measurement of ${}^4_\Lambda$H hypernucleus using in-flight ^{4}He(K^-, π^0)${}^4_\Lambda$H reaction. *Physics Letters B* **845,** 138128 (2023).

SUPERCONDUCTING DEVICES

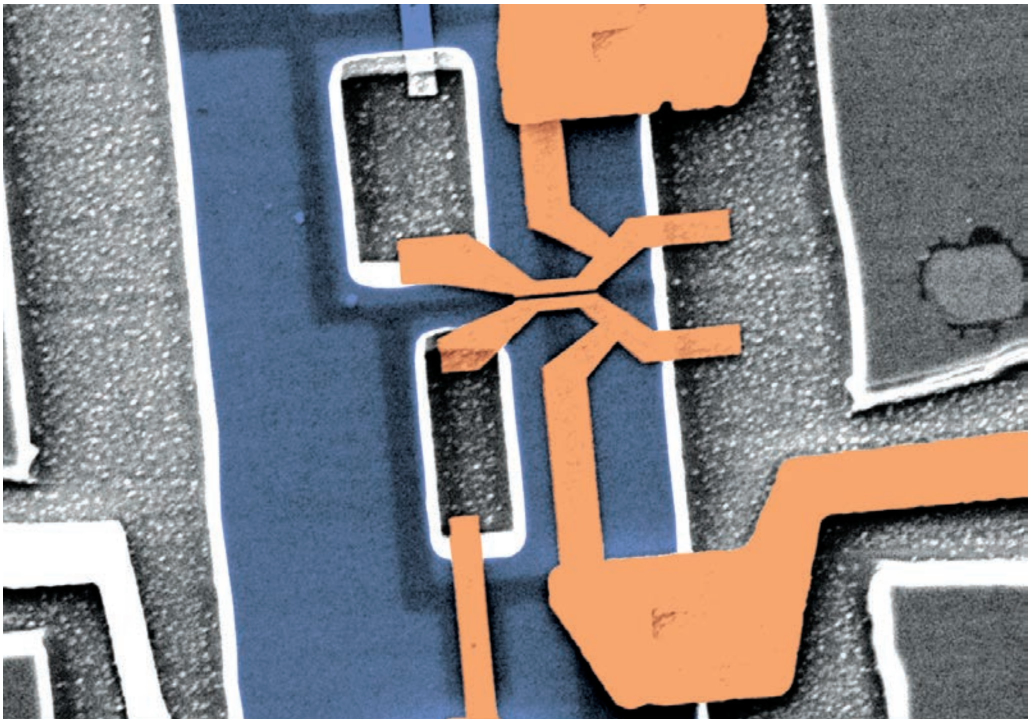
A one-way street for superconductivity

The superconducting equivalent of the diode has been realized using Josephson junctions, opening new possibilities for harnessing superconductivity in devices

RIKEN physicists have created a superconducting diode—a device that allows a supercurrent to flow in one direction but not the other[1]. While not the first time that such a device has been realized, this demonstration presents a new method for achieving it.

Superconductors, which allow electrical currents to flow without resistance, hold out exciting possibilities for electronics. That's because superconducting circuits and devices promise to harness a wide range of exotic phenomenon that aren't possible in conventional semiconductor-based devices. For example, they could be used as the basic building blocks of quantum computers.

One of the most important components in conventional silicon-based electronics is the diode—a device that lets current flow in one direction but not in the other.



Scanning electron microscopy image of the device, which uses two Josephson junctions to control the supercurrent flowing through one to the other.

An analogous concept, the superconducting diode effect also exists where the electrical resistance depends on which way the current is flowing. This effect was first demonstrated in 2020 by a group at Kyoto University and has subsequently been realized by many other groups.

Now, Sadashige Matsuo of the RIKEN Center for Emergent Matter Science and his co-workers have demonstrated the superconducting diode effect in a new way—by using two devices known as Josephson junctions (see image). In particular, they were able to use one junction to control the flow of a supercurrent in the other.

Josephson junctions consist of a thin film of a non-superconducting material sandwiched between two superconductors. Up to some critical current, electrons can cross the barrier without resistance in what is known as a supercurrent. Above the critical current, a conventional current can flow.

The key to realizing the superconducting diode effect was breaking symmetries in the device. "Symmetries, both those in space and time, in a superconducting device require that the critical currents in the two flow directions be the same," explains Matsuo. "By breaking these symmetries, the critical current in one direction can be different from one in the other direction." This is the superconducting diode effect.

Matsuo and team started by covering a thin but high-quality layer, known as a quantum well, of the semiconductor indium arsenide with a film of aluminum. On this platform, they then constructed two Josephson junctions that shared one superconducting electrode.

At a very low temperature, the team showed that phase control of one of the coupled junctions can break the time-reversal and spatial-inversion symmetries in the other junction.

The results provide a practical method for harnessing superconducting on a scalable electronic platform. "The next step is to use our coupled Josephson junctions to explore other exotic superconducting phenomena," says Matsuo. ●

Reference

1. Matsuo, S., Imoto, T., Yokoyama, T., Sato, Y., Lindemann, T., Gronin, S., Gardner, G. C., Manfra, M. J. & Tarucha, S. Josephson diode effect derived from short-range coherent coupling. *Nature Physics* **19,** 1636–1641 (2023).

BIOLOGICAL RHYTHMS

Revealing the rhythms of hair growth

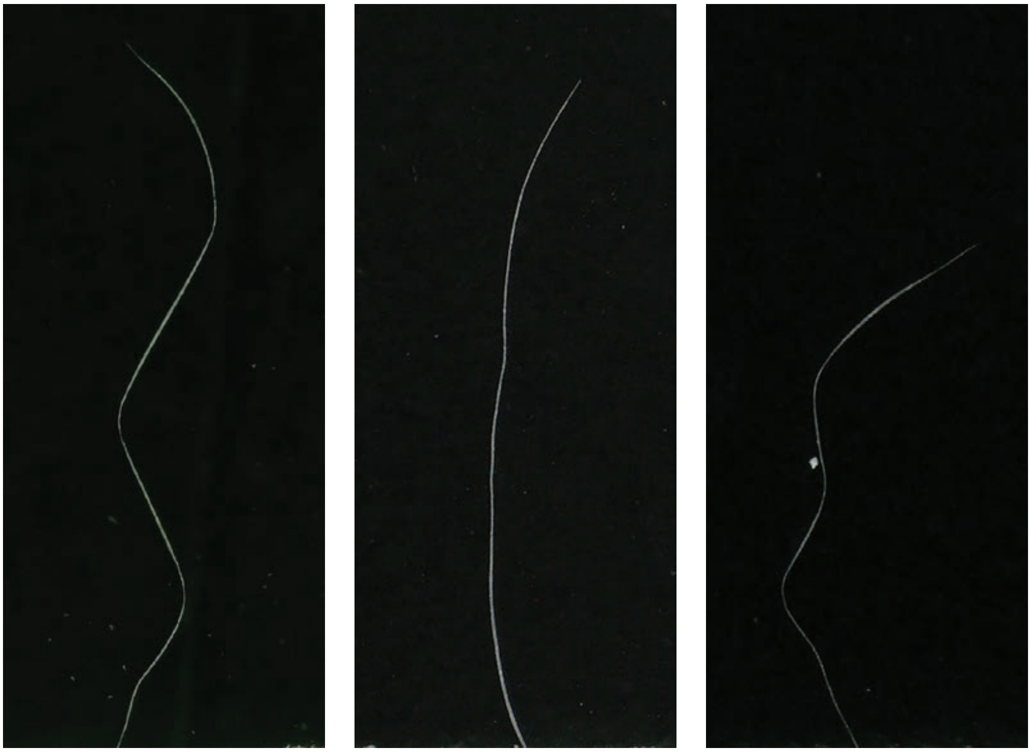
The molecular secrets behind 'zigzag' hair patterns might offer an avenue for anti-aging solutions

RIKEN researchers have discovered how biological rhythms influence hair growth in mice[1]. This finding could pave the way for novel anti-aging treatments in humans.

The sleep and menstrual cycles are two examples of the vast array of biological rhythms that underpin almost all biological processes. Since such biological rhythms play essential roles from an organism's beginnings to its old age, it is critical to gain insights into how they work. But not much is known about how such periodic cycles are sustained after birth.

Hair follicles in mammals provide an interesting system to explore biological rhythms since they are repeatedly regenerated in the hair cycle process.

A team led by Takashi Tsuji of the RIKEN Center for Biosystems Dynamics Research has been investigating the molecular mechanisms responsible for the distinctive bending pattern observed in 'zigzag hairs'. Found in the underfur of mice, these hairs develop kinks every three days during the follicle maturation process.



Microscopy images of zigzag hairs in an unaltered mouse (left), a mouse with two genes knocked out (center), and a mouse with two genes enhanced (right).

Now, the team has uncovered a molecular rhythm responsible for this hair-growth phenomenon.

Every three days, there was a noticeable shift in the spatial arrangement of progenitor cells located at the base of developing zigzag follicles in relation to support cells. These interactions were accompanied by cyclic fluctuations in biochemical signals.

This discovery could have practical applications. "By artificially controlling these molecules, it may be possible to regulate biological rhythms and potentially prevent age-related hair changes," says Tsuji. "This could lead to the development of new healthcare products."

Tsuji's team examined the interplay between two specialized cell types positioned at the base of hair follicles in genetically engineered mice. They found that the crosstalk between these cells orchestrates the three-day molecular rhythms in mouse fur, with synchronized alterations in the behavior of both cell types occurring just before bends formed in the zigzag hairs.

The researchers also pinpointed two genes associated with cell growth and survival that played a pivotal role in mediating these recurring physiological changes.

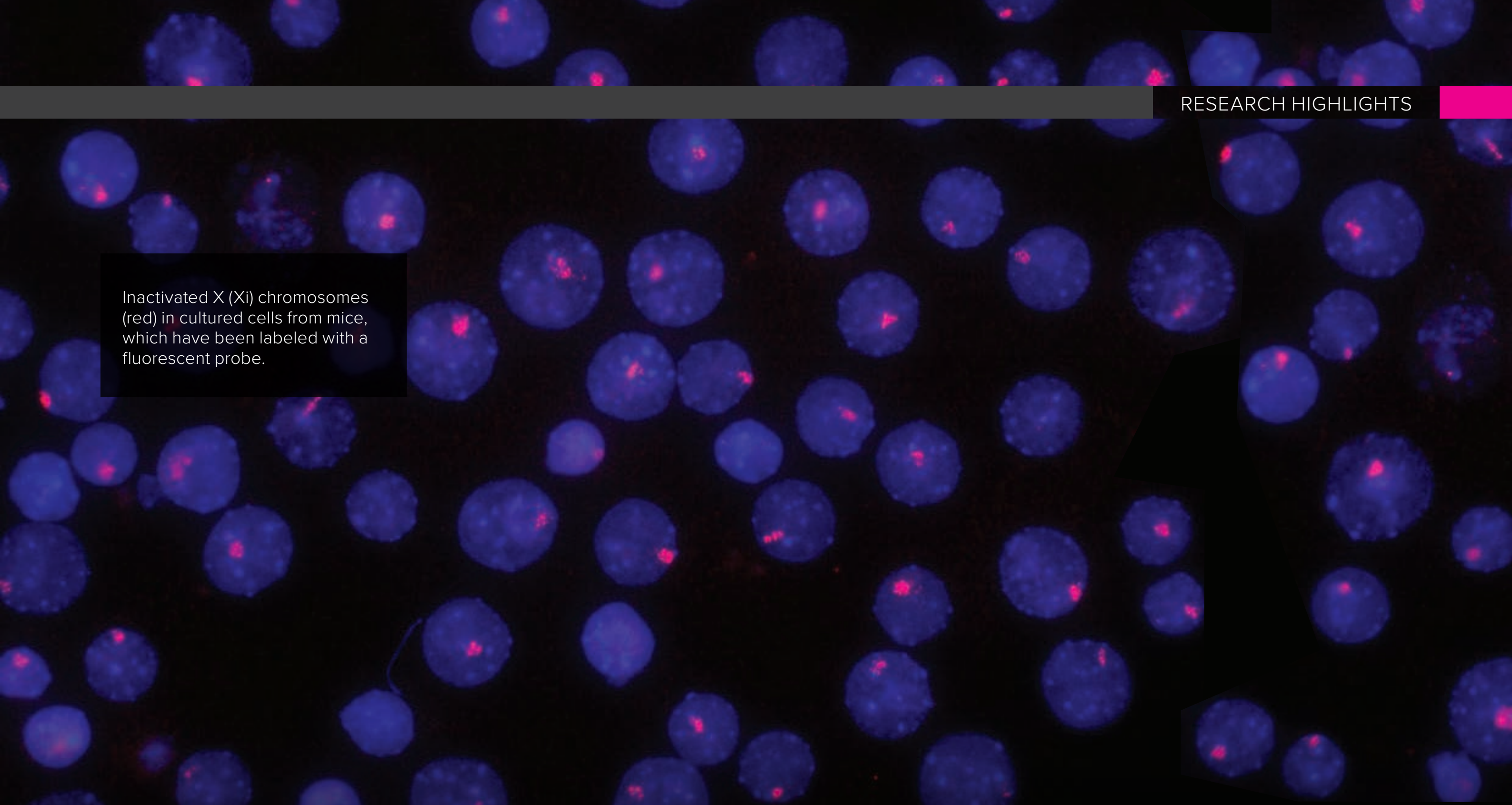
To investigate the significance of these genes, the researchers knocked them out in one experiment and artificially inflated expression levels in another (see image). In both instances, the genetic manipulations disrupted the molecular rhythms, resulting in a departure from the zigzag shape of the hairs.

The team next plans to look for similar rhythms in human-hair development.

"Variations in hair curvature exist among individuals and different ethnicities, generating significant interest in understanding the underlying biological rhythm," Tsuji says. "If we can unravel this puzzle, it might enable us to manipulate human hair morphology at will and potentially halt age-related changes." ●

Reference

1. Takeo, M., Toyoshima, K.-e., Fujimoto, R., Iga, T., Takase, M., Ogawa, M. & Tsuji, T. Cyclical dermal micro-niche switching governs the morphological infradian rhythm of mouse zigzag hair. *Nature Communications* **14,** 4478 (2023).



Inactivated X (Xi) chromosomes (red) in cultured cells from mice, which have been labeled with a fluorescent probe.

INACTIVE X CHROMOSOME

Uncovering the secrets of a quiescent chromosome

Sophisticated techniques offer insights into the inactive X chromosome in female mammalian cells

RIKEN cell biologists have provided an unprecedented glimpse into the distinctive features of an unusual chromosome—an inactivated X chromosome copy carried by every female cell[1].

Not all X chromosomes are created equal. In every cell of female mammals, one of the two X chromosome copies is compacted into an inactive form known as the inactive X chromosome (Xi). It differs in both structure and function from its active counterpart, and other chromosomes.

Unlike most chromosomes, which replicate gradually throughout the hours-long 'S phase' stage of cell division, the Xi is copied in the latter half of this phase. Researchers have hypothesized that this replication behavior is closely tied to the unusual structure of the Xi, which is more uniform and compact than other chromosomes.

"However, this was still uncertain when we started our research," says Rawin Poonperm of the RIKEN Center for Biosystems Dynamics Research (BDR). "We thought that a detailed analysis of the Xi's replication timing might uncover its purpose as well as provide new insights into its 3D organization."

The researchers used two cutting-edge analytical methods to address this question by differentiating cultured embryonic stem cells from mice. The first, which was developed by a group led by Ichiro Hiratani (also of BDR), precisely determined the timing of when specific chromosomal sequences undergo replication. In parallel, they employed a second technique, which revealed the 3D structure of chromatin—the combination of DNA and protein that forms chromosomes—thereby offering insights into gene expression activity.

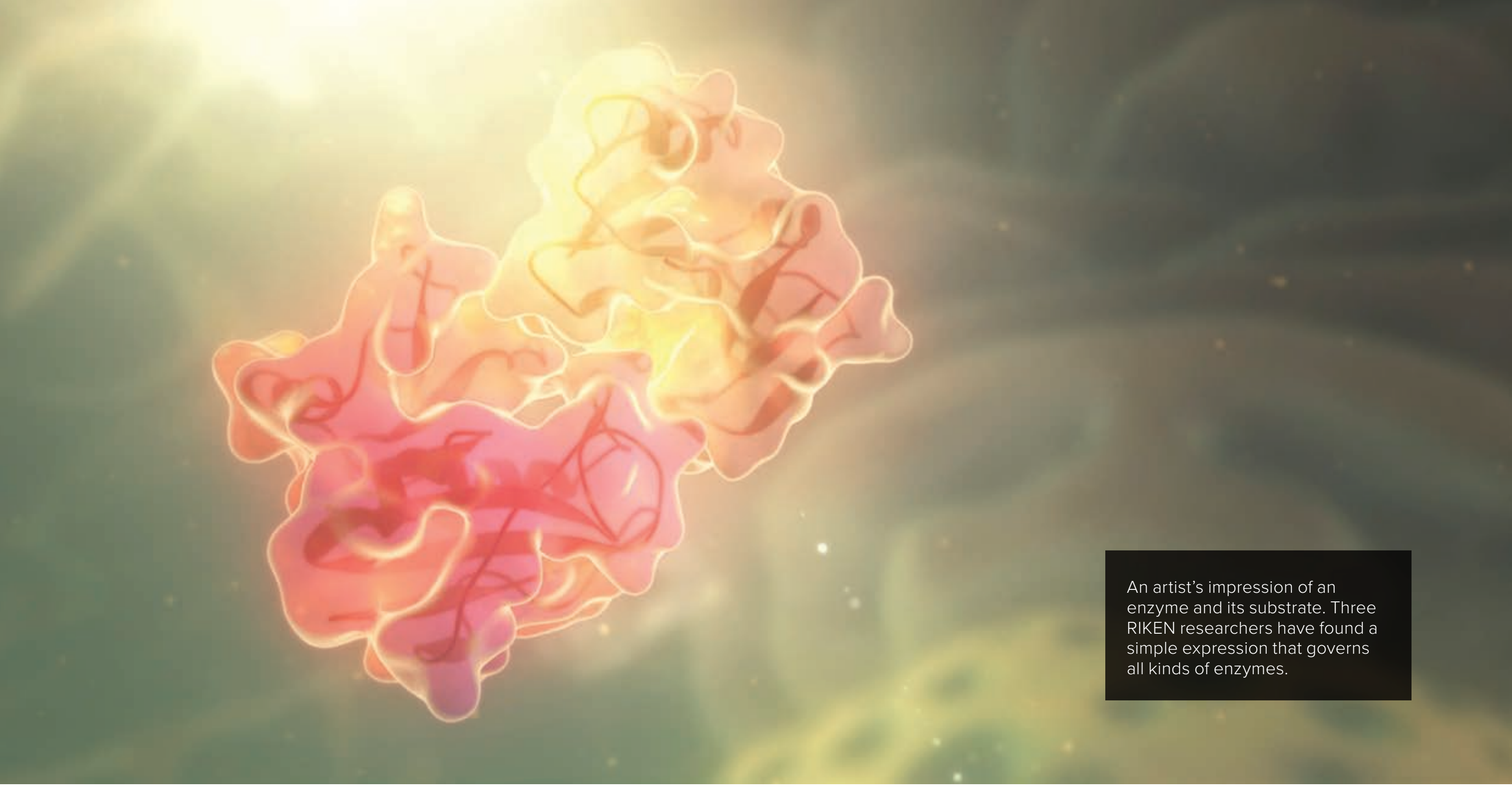
This combination of the two techniques proved highly effective. "Our high-resolution replication analysis revealed that the Xi is copied quickly within the second half of the S-phase. Moreover, our 3D structure results showed that dynamic changes in the replication timing of the Xi closely corresponded to changes in chromatin organization during differentiation," says Poonperm. She adds that their structural analysis of the Xi chromosome also revealed some surprises, including differences in the magnitude of compaction and inactivation at different sites in the chromosome.

When the researchers analyzed differentiated cells that lacked a gene called SmcHD1, which helps keep the Xi inactive, they observed reactivation of normally dormant genes at the edge of the chromosome. Most other Xi genes remained quiescent, however, hinting at hidden structural complexity in this seemingly uniform chromosome.

Hiratani's group next plans to examine the process of X chromosome inactivation itself. This will entail considerably more challenging experiments in actual mouse embryos rather than cultured embryonic stem cells. But Poonperm sees an exciting opportunity to resolve mysteries that have surrounded this process for decades. "We firmly believe that there are more surprising discoveries to be made," she says. ●

Reference

1. Poonperm, R., Ichihara, S., Miura, H., Tanigawa, A., Nagao, K., Obuse, C., Sado, T. & Hiratani, I. Replication dynamics identifies the folding principles of the inactive X chromosome. *Nature Structural and Molecular Biology* **30**, 1224–1237 (2023).



An artist's impression of an enzyme and its substrate. Three RIKEN researchers have found a simple expression that governs all kinds of enzymes.

ENZYMES

Simple relation for optimizing enzyme reaction rates

A surprisingly simple expression for enzyme activity could help guide biotechnologists

A surprising relationship that governs the activity of enzymes—the molecules that catalyze almost all the chemical reactions of life—has been uncovered by three RIKEN researchers[1]. This finding could help researchers to select and design the best enzymes for use in biotechnology applications.

All forms of life depend on enzymes—without them most biochemical reactions would proceed too slowly to sustain the processes of life. Enzymes function by binding to a compound known as a substrate.

The activity of enzymes—a measure of how much they speed up a reaction—is commonly described mathematically by considering three rates: the rate at which the substrate molecules bind to the enzyme; the rate at which that binding can be reversed; and the rate at which the substrate is converted into the reaction's product.

Each of these three steps is characterized by a numerical rate constant. When these constants are combined in an equation, a value called K_m emerges. This reflects the affinity of the enzyme for its substrate, with lower K_m values indicating higher affinity.

The RIKEN trio's mathematical analysis revealed a surprisingly simple relationship between an enzyme's K_m value and the conditions in which it will be the most active enzyme among enzymes that catalyze the same reaction.

"Theory predicts that the best enzyme is one that has a K_m equal to the substrate concentration," says Hideshi Ooka of the RIKEN Center for Sustainable Resource Science. "We started this research knowing that we would obtain some kind of formula for maximum activity, but we never expected it to be so concise. For me, the simplicity felt beautiful in a mathematical sense."

This insight led the team to explore existing data for the relationship between K_m and substrate concentrations in nature. The results supported their hypothesis: a survey of more than 1,000 enzymes revealed that many operate in surroundings in which the concentration of their substrate was equal to, or very close to, their individual K_m values.

"This suggests that one direction of biological evolution was to ensure that the K_m values of enzymes are close to the substrate concentrations in their natural environment," says Ooka.

While offering an important new understanding of enzyme evolution, this insight will also help researchers to modify or design enzymes for use in biotechnology.

> "For me, the simplicity felt beautiful in a mathematical sense."

"One key takeaway message is that K_m should not be too small, contradicting a previous assumption that a small K_m is always better," Ooka says. "Instead, choosing or designing enzymes with K_m values equal to the substrate concentrations they will have to work with will be the best strategy." ●

Reference

1. Ooka, H., Chiba, Y. & Nakamura, R. Thermodynamic principle to enhance enzymatic activity using the substrate affinity. *Nature Communications* **14**, 4860 (2023).

OVARIAN CANCER

Big data reveals targets for treating ovarian cancer

A better understanding of genes involved in ovarian cancer development could lead to new treatments

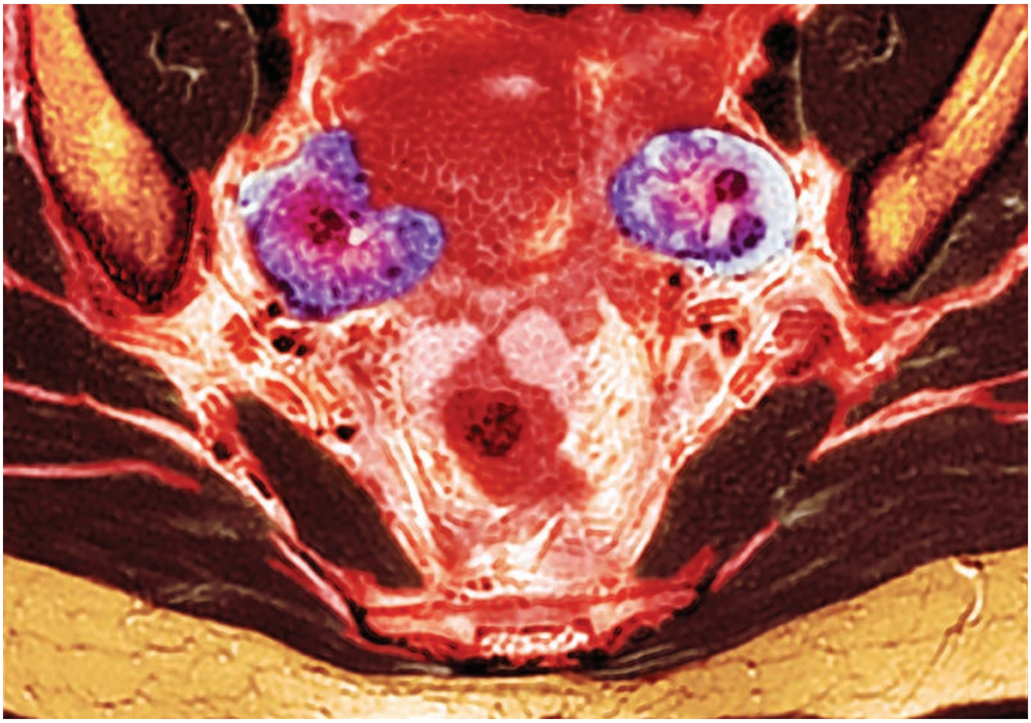
Using big data, RIKEN researchers have discovered changes in gene expression that occur as cells in human fallopian tubes become cancerous[1]. Based on this, they predicted an effective treatment and tested it, with promising results.

Ovarian cancer is one the most challenging cancers affecting the female reproductive system, with high-grade serous ovarian carcinoma (HGSOC) being the deadliest.

One reason why it is so difficult to treat is because it is driven by more than one genetic mutation. So rather than looking at DNA sequences, the team focused on epigenetic profiles—the on/off switches within a specific cell type that affect gene expression and, in this case, lead to tumor formation.

HGSOC originates in the fallopian tubes, with the most difficult cases being unresponsive to chemotherapy. The researchers focused on this type of tumor using cells derived from the cells that line human fallopian tubes. They grew these cells under various conditions and then studied them using a special integrative omics analysis.

"This analysis integrates and analyzes a huge amount of data from multiple high-throughput techniques to gain a holistic understanding of complex biological systems," explains Hidenori Machino of the RIKEN Center for Advanced Intelligence Project.



Magnetic resonance imaging (MRI) scan showing two ovarian cancer tumors (purple areas). RIKEN researchers have used big data to find out how gene expression changes as cells in human fallopian tubes become cancerous.

DR P. MARAZZI / SCIENCE PHOTO LIBRARY

The multi-omics analysis predicted that specific factors controlling gene expression start behaving abnormally just when cells switch to being cancerous. These predictions were confirmed by comparing protein levels between normal and cancerous cells.

Specifically, the researchers found that proteins that help spur the growth and spread of cancer cells were overly active in cancerous cells. Additionally, proteins that usually help control cell behavior were less effective in cancerous cells.

The analysis also identified three genes that play a crucial role in controlling cancer growth. During the early stages of tumor development, these genes were epigenetically suppressed, contributing to tumor formation.

Based on these findings, the researchers proposed a countermeasure. "We realized that the culprit was excessive Ras activation as a result of the epigenetic gene suppression," says Machino. "And we reasoned that a drug which can block events in this pathway would reverse the trend."

When tested with trametinib, a clinically applicable drug that can inhibit Ras signaling, they observed signs of normal epigenetic control.

This study predicts that drugs like trametinib could be effective in preventing tumorigenesis in ovarian cancer. "The findings point to new therapeutic approaches, which could have a significant impact on society," says Machino.

Furthermore, the three genes they found could be useful biomarkers. "The HGSOC biomarkers we discovered have the potential to be used for early detection of ovarian cancer," says Machino. ●

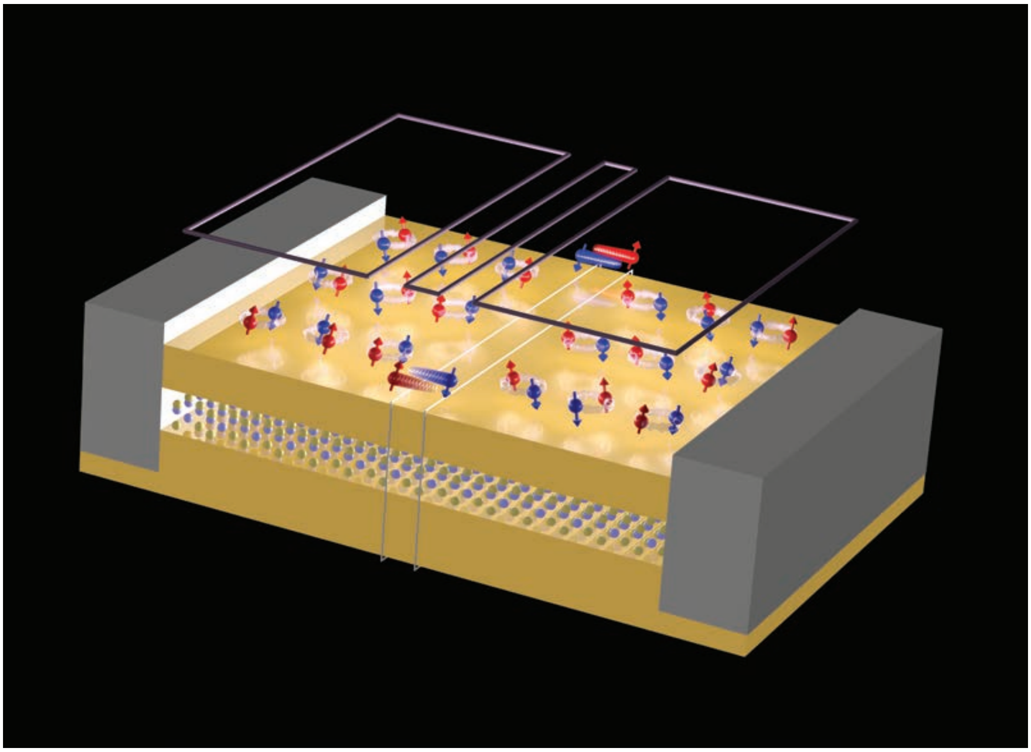
Reference

1. Machino, H., Dozen, A., Konaka, M., Komatsu, M., Nakamura, K., Ikawa, N., Shozu, K., Asada, K., Kaneko, S., Yoshida, H. *et al.* Integrative analysis reveals early epigenetic alterations in high-grade serous ovarian carcinomas. *Experimental & Molecular Medicine* **55,** 2205–2219 (2023).

QUANTUM MATERIALS

Making a quantum sandwich from just one material

A superconducting junction made from a single 2D material promises to harness strange new physics



A schematic image showing a Josephson junction (central section) made from a single layer of tungsten telluride. The red spheres are electrons with spin up, while the blue ones have spin down.

Physicists at RIKEN have developed an electronic device that hosts unusual states of matter, which could one day be useful for quantum computation[1].

When a material exists as an ultrathin layer—a mere one or a few atoms thick—it has totally different properties from thicker samples of the same material. That's because confining electrons to a 2D plane gives rise to exotic states. Because of their flat dimensions and their broad compatibility with existing semiconductor technologies, such 2D materials are promising for harnessing new phenomenon in electronic devices.

These states include quantum spin Hall insulators, which conduct electricity along their edges but are electrically insulating in their interiors. Such systems when coupled with superconductivity have been proposed as a route toward engineering topological superconducting states that have potential application in future topological quantum computers.

Now, Michael Randle at the RIKEN Advanced Device Laboratory, along with co-workers from RIKEN and Fujitsu, have created a 2D Josephson junction with active components entirely from a material known to be a quantum spin Hall insulator (see image).

A Josephson junction is generally made by sandwiching a material between two elemental superconductors. In contrast, Randle and team fabricated their device from a single crystal of monolayer 2D tungsten telluride, which had previously been shown to exhibit both a superconducting state and a quantum spin Hall insulator one.

"We fabricated the junction entirely from monolayer tungsten telluride," says Randle. "We did this by exploiting its ability to be tuned into and out of the superconducting state using electrostatic gating."

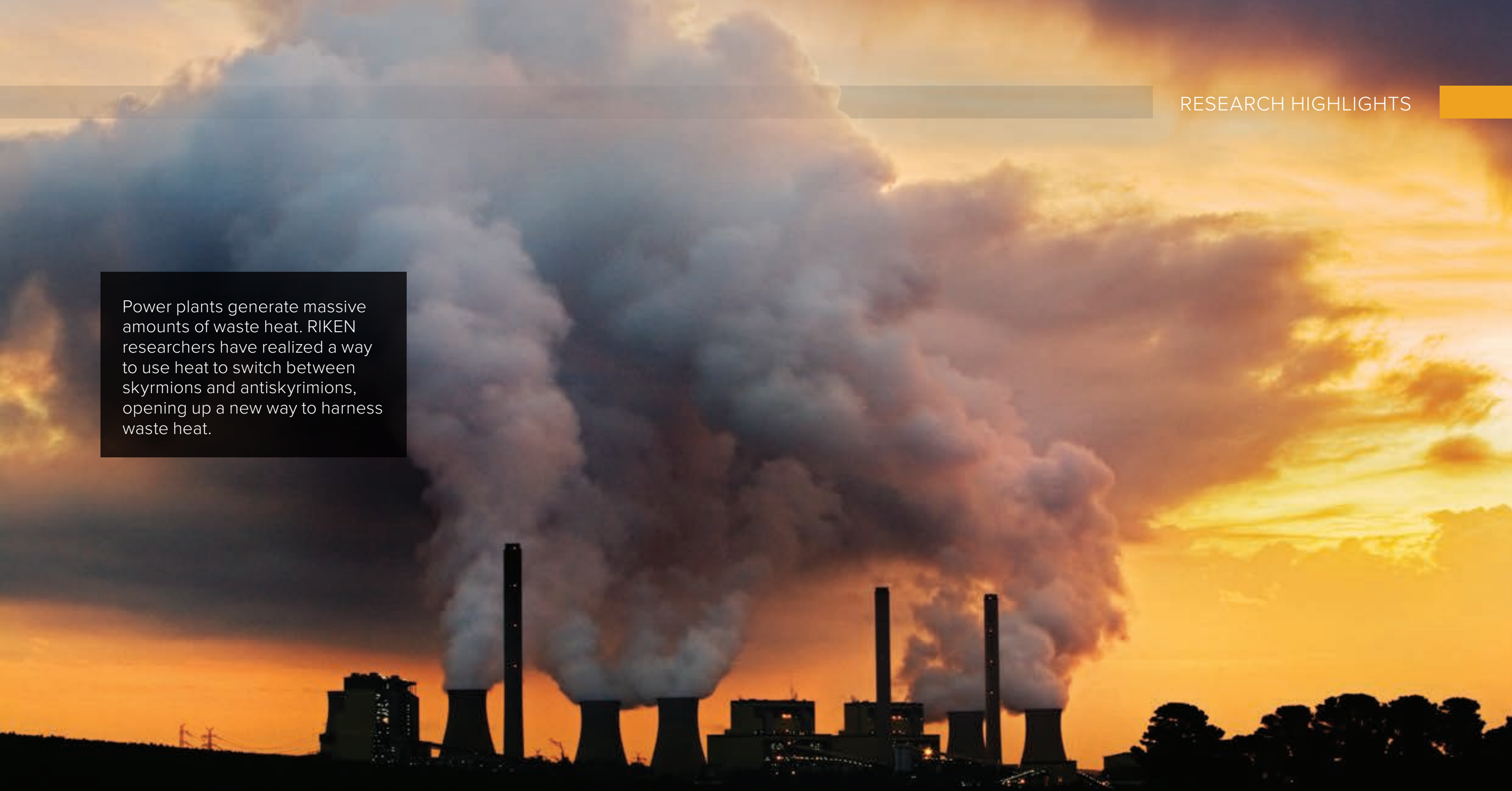
The team used thin layers of palladium to connect to the sides of a tungsten telluride layer surrounded and protected by boron nitride. They were able to observe an interference pattern when they measured the sample's magnetic response, which is characteristic of a Josephson junction with 2D superconducting leads.

While this study provides a framework for understanding complex superconductivity in 2D systems, further work is required to clearly identify the more exotic physics the systems promise. The challenge is that tungsten telluride is difficult to process into devices due to the rapid oxidization within minutes of its surface under ambient conditions, which requires all fabrication to be performed in an inert environment.

"The next step involves the implementation of ultraflat pre-patterned gate structures by using, for example, chemical–mechanical polishing," explains Randle. "If this is achieved, we hope to form Josephson junctions with precisely tailored geometries and to use our cutting-edge microwave resonator experiment techniques to observe and investigate the exciting topological nature of the devices." ●

Reference

1. Randle, M. D., Hosoda, M., Deacon, R. S., Ohtomo, M., Zellekens, P., Watanabe, K., Taniguchi, T., Okazaki, S., Sasagawa, T., Kawaguchi, K. *et al.* Gate-defined Josephson weak-links in monolayer WTe_2. *Advanced Materials* **35,** 2301683 (2023).



Power plants generate massive amounts of waste heat. RIKEN researchers have realized a way to use heat to switch between skyrmions and antiskyrimions, opening up a new way to harness waste heat.

SKYRMIONS

Just heat to switch between skyrmions and antiskyrmions

Waste heat could be used to power ultralow energy data-storage devices based on skyrmions

In an advance that could aid the development of new low-energy-consumption devices, RIKEN researchers have used heat and magnetic fields to convert tiny magnetic vortices into their antivortices, and vice versa[1]. Importantly, they achieved this at room temperature.

Skyrmions and antiskyrmions are tiny magnetic whirlpools of electron spins in special magnetic materials. They are an active area of research, as they could be used for next-generation memory devices.

Scientists can move them in various ways and create transformations between them using an electric current. However, modern electronic devices consume electrical power and produce waste heat.

A team led by Xiuzhen Yu of the RIKEN Center for Emergent Matter Science (CEMS) decided to see if they could find a way to create the transformations using heat gradients.

“Approximately two-thirds of the energy produced by power plants, automobiles, incinerators, and factories is wasted as heat. So we thought it would be important to try to create transformations between skyrmions and antiskyrimions—which has previously been done via electric current—using heat,” explains Yu.

Using an extremely precise fabrication system, the team created a microdevice from the bulk single-crystal magnet composed of iron, nickel, palladium, and phosphorous atoms. They then examined its magnetic properties at tiny scales.

When a temperature gradient was applied to the crystal simultaneously with a magnetic field, at room temperature, the antiskyrmions within it transformed first into a sort of transition state between skyrmions and antiskyrmions—and then to skyrmions, as the temperature gradient was raised. They remained in a stable configuration as skyrmions even after removing the thermal gradient.

A second finding surprised the group. “We were surprised to also find that when the magnetic field was not applied, the thermal gradient led to a transformation from skyrmions to antiskyrmions, which also remained stable within the material,” says Fehmi Yasin, also of CEMS. “What is very exciting about this is that this means we could use a thermal gradient—basically using waste heat—to drive a transformation between skyrmions and antiskyrmions, depending on whether a magnetic field is applied or not.”

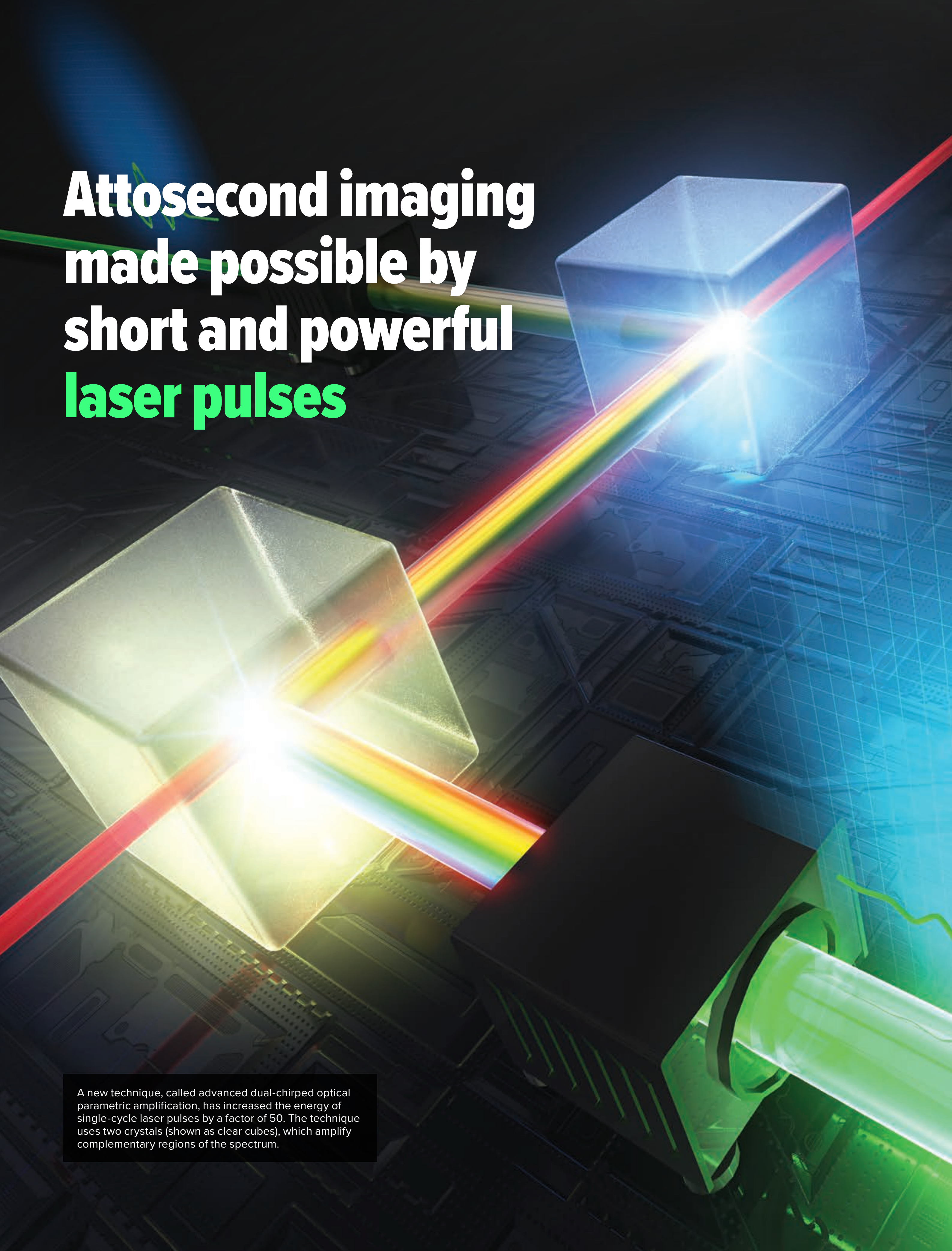
Critically, they were able to do this at room temperature. “This could open the way to a new type of information storage device such as nonvolatile memory devices using waste heat,” says Yasin.

“We’re very excited about this finding, and plan to continue our work to manipulate skyrmions and antiskyrmions in new and more efficient ways, including the thermal control of antiskyrmion motion, with the goal to build actual thermospintronic and other spintronics devices that could be used in our everyday lives,” says Yu.

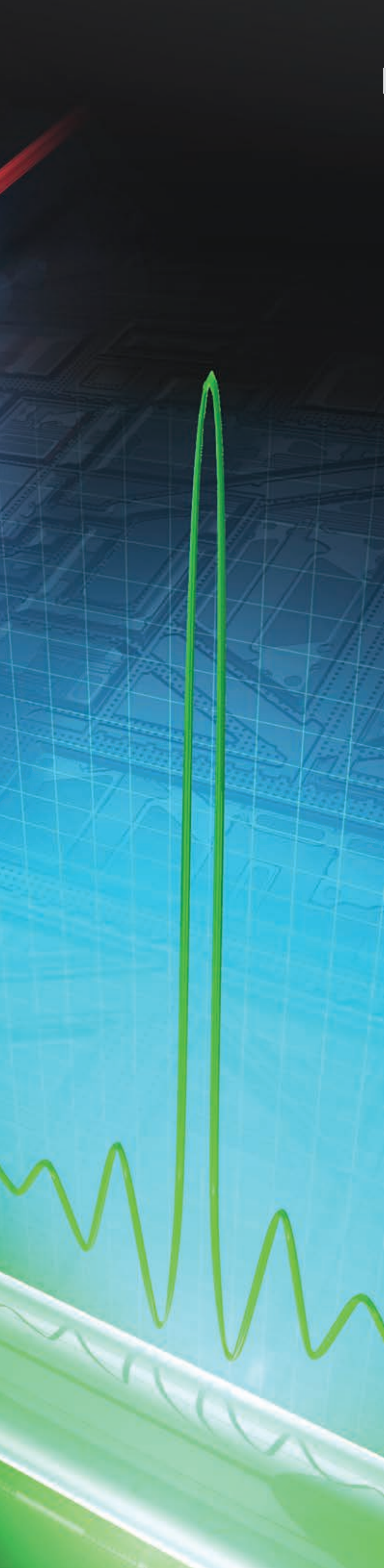
Reference

1. Yasin, F. S., Masell, J., Karube, K., Shindo, D., Taguchi, Y., Tokura, Y. & Yu, X. Heat current-driven topological spin texture transformations and helical q-vector switching. *Nature Communications* **14,** 7094 (2023).

Attosecond imaging made possible by short and powerful laser pulses



A new technique, called advanced dual-chirped optical parametric amplification, has increased the energy of single-cycle laser pulses by a factor of 50. The technique uses two crystals (shown as clear cubes), which amplify complementary regions of the spectrum.



A pair of nonlinear crystals is all it takes to create ultrashort laser pulses that are 50 times more energetic than any other laser pulses, finally shining light on how ultrafast electron reactions evolve.

This feature looks **at the work of** **EIJI J. TAKAHASHI**

Eiji Takahashi is the team leader of the Ultrafast Coherent Soft X-ray Photonics Research Team at the RIKEN Center for Advanced Photonics, and a chief scientist at the Extreme Laser Science Laboratory at the RIKEN Cluster for Pioneering Research. He received his Ph.D. in engineering at Utsunomiya University, Utsunomiya, Japan, in 2001. After this, he worked on the early development of intense high-order harmonic sources and spectroscopy at RIKEN. In 2004, he joined the Institute for Molecular Science, a research institute near Nagoya in Japan, where he was an assistant professor. Since rejoining RIKEN in 2006, Takahashi has researched novel ultrafast laser sources, such as optical waveform synthesizers, coherent soft x-rays, and attosecond lasers. His research interests include high-intensity laser-matter interactions, attosecond science, and high-power laser technology.

Extremely short pulses of laser light with a peak power of 6 terawatts (6 trillion watts)—roughly equivalent to the power produced by 6,000 nuclear power plants—have been realized by two RIKEN physicists[1]. This achievement will help further develop attosecond lasers, for which three researchers were awarded the Nobel Prize in Physics in 2023.

In the same way that a camera flash can ‘freeze’ rapidly moving objects, making them appear as if they are standing still in photos, extremely short laser pulses can help light up ultrafast processes, providing scientists with a powerful way to image and probe them.

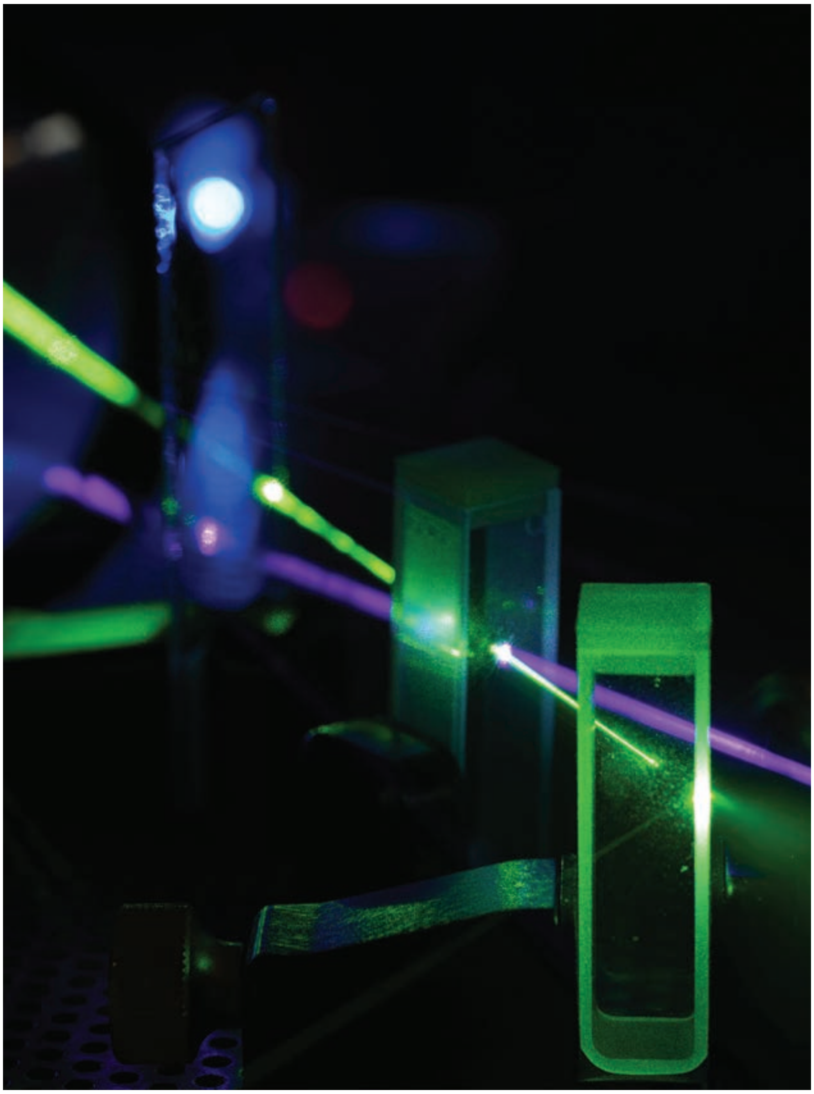
For example, laser pulses of the order of attoseconds (one attosecond = 10^{-18} second) are so short that they can reveal the motion of electrons in atoms and molecules, giving a new way to discover how chemical and biochemical reactions evolve. Even light seems to crawl at such short time scales, taking about 3 attoseconds to traverse a single nanometer.

“By making it possible to capture the motion of electrons, attosecond lasers have made a major contribution to basic science,” says Eiji Takahashi of the RIKEN Center for Advanced Photonics (RAP). “They’re expected to be used in a wide range of fields, including observing biological cells, developing new materials and diagnosing medical conditions.”

POWER AND PUNCH

But while it is possible to create ultrashort laser pulses, they lack much punch, having low energies. Creating laser pulses that are both ultrashort and have high energies would greatly expand their possible uses. “The current output energy of attosecond lasers is extremely low,” says Takahashi. “So it’s vital to increase their output energy if they are to be used as light sources in a wide range of fields.”

Just as audio amplifiers are used to boost sound signals, laser physicists use optical amplifiers to increase the energy of laser pulses. These amplifiers usually employ nonlinear crystals that exhibit special responses to light. But these crystals can be irreparably damaged if they are used to amplify single-cycle lasers pulses, which are so short that the pulse



RIKEN researchers have made a breakthrough in high-energy ultrafast lasers.

finishes before the light can oscillate through a full wavelength cycle.

"The biggest bottleneck in the development of energetic, ultrafast infrared laser sources has been the lack of an effective method to directly amplify single-cycle laser pulses," explains Takahashi. "This bottleneck has resulted in a one-millijoule barrier for the energy of single-cycle laser pulses."

A NEW RECORD

Now, Takahashi and RAP colleague, Lu Xu, have not just exceeded this barrier, they have smashed through it. They have amplified single-cycle pulses to beyond 50 millijoules—more than 50 times the best effort. Because the resulting laser pulses are so short, this energy translates into incredibly high powers of several terawatts. "We've demonstrated how to overcome the bottleneck by establishing an effective method for amplifying a single-cycle laser pulse," says Takahashi.

Their method, called advanced dual-chirped optical parametric amplification (DC-OPA), is surprisingly simple, involving just two crystals, which amplify complementary regions of the spectrum. "Advanced DC-OPA for amplifying a single-cycle laser pulse is very simple, being based on just a combination of two kinds of nonlinear crystals—it feels like an idea that anyone could have come up with," says Takahashi. "I was surprised that such a simple concept provided a new amplification technology and caused a breakthrough in the development of high-energy ultrafast lasers."

Importantly, advanced DC-OPA works over a very broad range of wavelengths. Takahashi and Xu were able to amplify pulses whose wavelengths differed by more than a factor of two. "This new method has the revolutionary feature that the amplification bandwidth can be made ultrawide without compromising the output energy-scaling characteristics," says Takahashi.

AMPLIFICATION TECHNIQUE

Their technique is a variation on another amplification technique for optical pulses, called 'chirped pulse amplification', for which three researchers from the United States, France and Canada were awarded the Nobel Prize in Physics in 2018. There is an interesting connection between the 2018 and 2023 prizes in that chirped pulse amplification was one of the techniques that enabled the development of attosecond lasers.

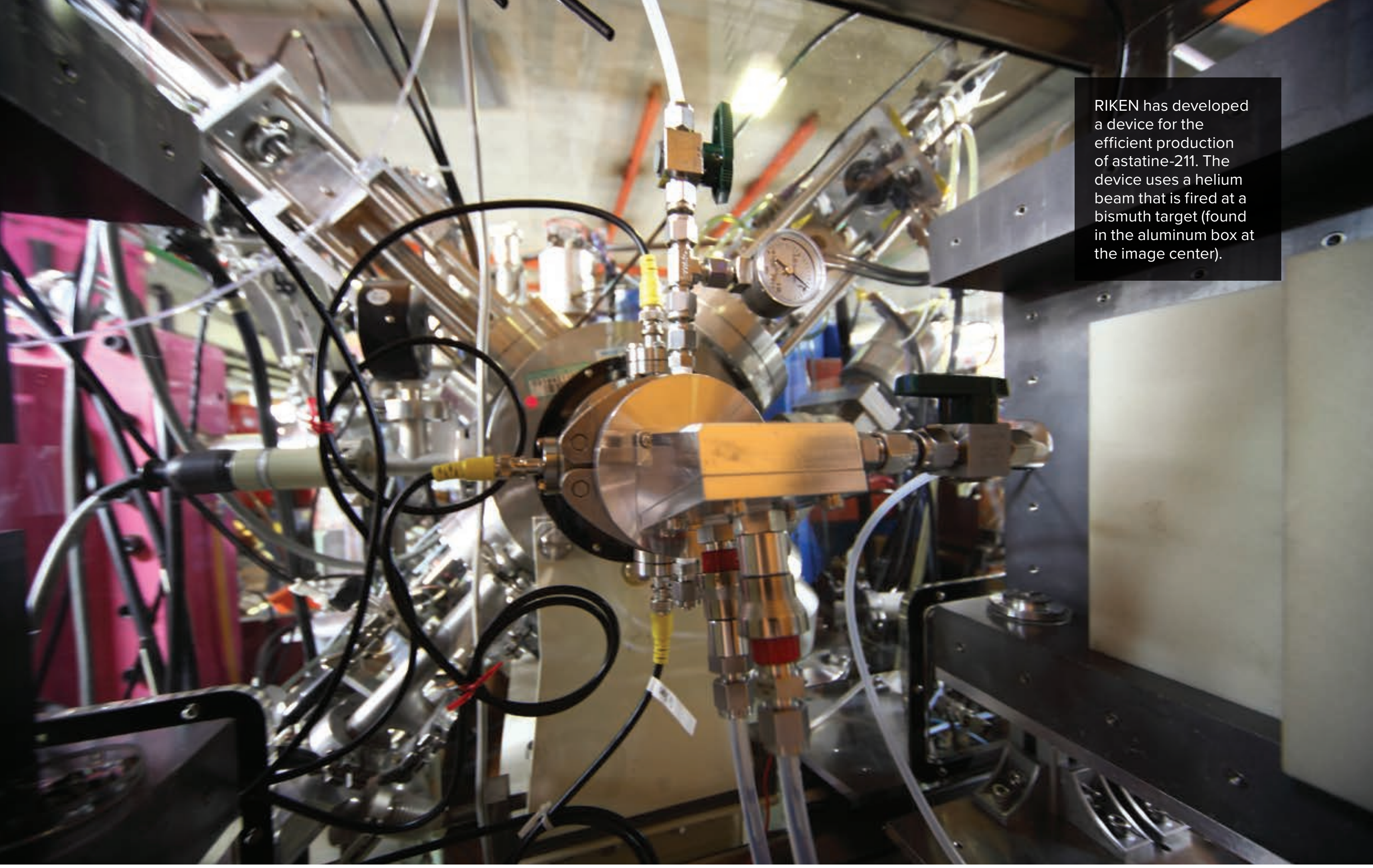
Takahashi anticipates that their technique will further advance the development of attosecond lasers. "We have succeeded in developing a new laser amplification method that can increase the intensity of single-cycle laser pulses to terawatt-class peak power," he says. "It's undoubtedly a major leap forward in the development of high-power attosecond lasers."

In the longer term, he has his sights set on going beyond attosecond lasers and creating even shorter pulses.

"By combining single-cycle lasers with higher-order nonlinear optical effects, it could well be possible to generate pulses of light with a time width of zeptoseconds (one zeptosecond = 10^{-21} second)," he says. "My long-term goal is to knock on the door of zeptosecond-laser research, and open up the next generation of ultrashort lasers after attosecond lasers." ●

REFERENCE

Xu, L. & Takahashi, E. J. Dual-chirped optical parametric amplification of high-energy single-cycle laser pulses *Nature Photonics* **18**, 99–106 (2024).



RIKEN has developed a device for the efficient production of astatine-211. The device uses a helium beam that is fired at a bismuth target (found in the aluminum box at the image center).

Building capacity to beat cancer with a targeted radiopharmaceutical

RIKEN's particle accelerator facilities are producing astatine-211, a radioisotope with great promise for selective anti-tumor therapies, says Hiromitsu Haba.

The suite of powerful particle accelerators at RIKEN has a long history of dual-purpose use. As well as the central role these instruments play in fundamental nuclear physics research, they have also long been employed in the production of valuable radioisotopes.

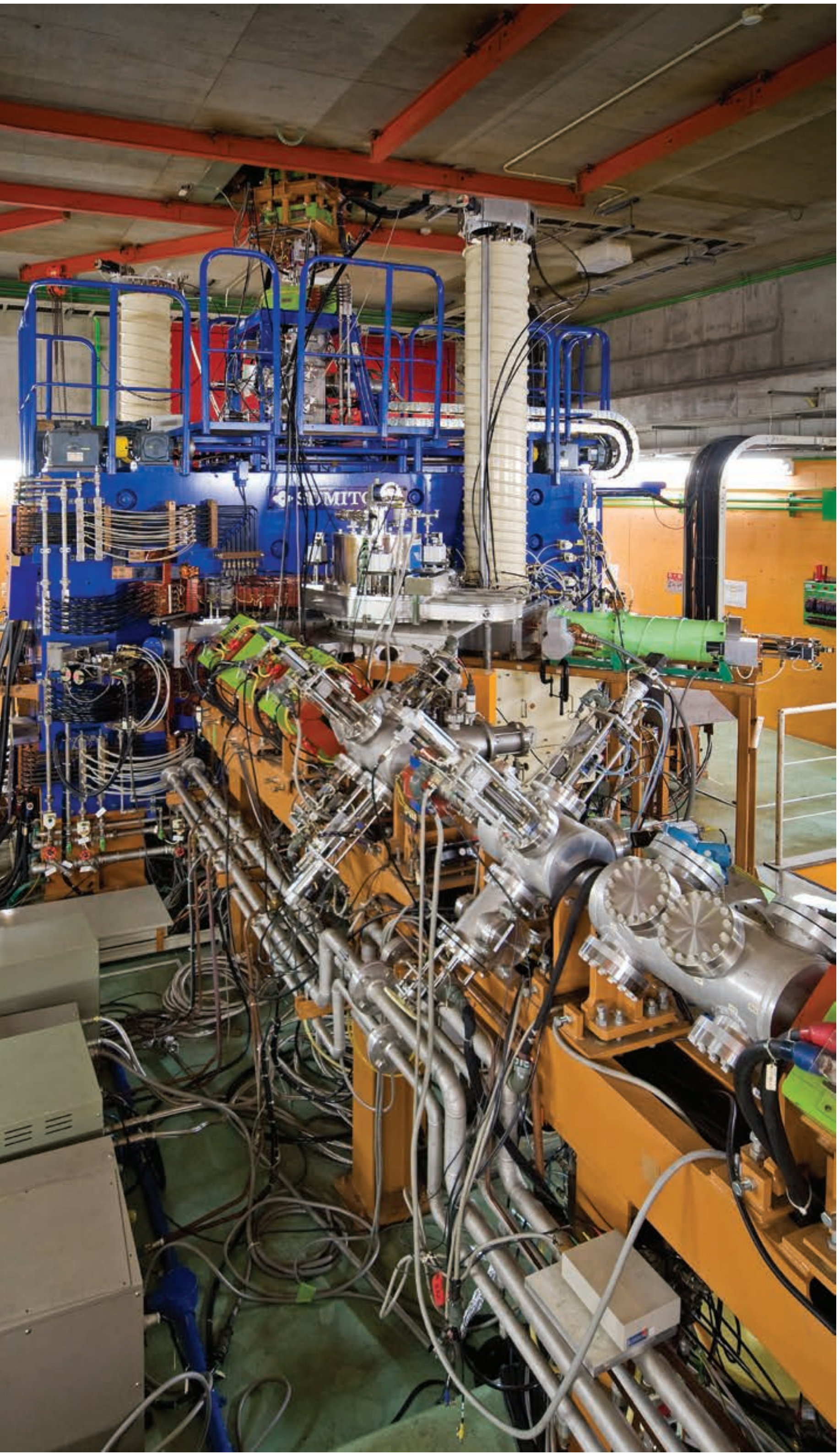
Today, some of the strongest radioisotope demand comes from medicine, where they are used in imaging and increasingly, as cancer treatments. Currently, there is a rapidly growing interest in astatine-211, a promising radioisotope for the potential selective treatment of numerous cancers.

Fortunately, innovative new methods for producing astatine-211 in practical amounts have recently been pioneered at our facility. And, a recently launched human clinical trial at Osaka University Hospital of an astatine-211 based anticancer radiopharmaceutical, a first for Japan, is leveraging these new production abilities.

TRADITIONAL STRENGTHS

Radioisotopes are atoms that have an unstable nucleus, and so shed excess energy as radiation in a process called radioactive decay. These active chemical species have numerous applications across research, industry, and medicine.

At RIKEN, this potential was recognized early. In 1937, one of the world's first cyclotron particle accelerators was built at RIKEN by renowned physicist Yoshio Nishina. Within a year, Nishina was using the cyclotron to produce valuable radioisotopes to trace the behavior of elements in chemical reactions and plants, in addition to his nuclear physics research. Today our facility, the RIKEN Nishina Center for



Researchers are making the astatine-211 radioisotope by using particle accelerators such as the RIKEN Azimuthally Varying Field (AVF) Cyclotron to fire a beam of helium-4 particles into a bismuth target.

Accelerator-Based Science, is named in his honor, and the dual function that Nishina introduced remains.

In the research realm, a superheavy chemical element called nihonium—the first element ever discovered in Asia—was first synthesized in our facility in 2004, and our fundamental research into superheavy element synthesis remains active.

On the application side, our radioisotope production expertise has continued to expand. We now produce more than 100 radioisotopes, covering all regions of the periodic table. We collaborate with researchers around the world to conduct radioisotope application studies in the fields of physics, chemistry, biology, engineering, environmental science, and medicine.

In the medical field, there is rapidly increasing interest in astatine-211 as a potential cancer therapy. This radioisotope decays by emitting an alpha particle, which characteristically delivers a large amount of energy over a short distance.

In the human body, an alpha particle shed by astatine-211 will typically travel a distance of no more than two or three cells. Thus, if we can incorporate astatine-211 into a medicine that selectively accumulates in cancer cells, we could create a therapeutic that is highly cytotoxic to cancer cells, but has minimal toxicity to healthy cells. This research could result in new anticancer medicines with high efficacy but few side effects.

COOL OPERATIONS

In Japan, demand for astatine-211 is increasing rapidly. This isotope does not exist in nature, but it can be produced by particle accelerators. We produce it by firing a beam of helium-4 particles into a target of solid metallic bismuth. Helium has an atomic number of two, and bismuth an atomic number of 83. When the two atomic nuclei combine, they form the element with atomic number 85: astatine.

The key challenge with astatine-211 production is that metallic bismuth has a relatively low melting point, liquifying at just 271°C. The helium-4 particle beam generates a lot of heat and melts the bismuth target. To increase our production rate to meet growing demand, we introduced several process modifications to minimize the heating effect.

We orient the bismuth target at an angle of 10° to the beam axis, and use helium gas and flowing water to cool the front and back of the target, respectively. We also use a beam wobbling system to continually sweep the beam across the target, avoiding local heating of the beam spot on the target.

With this system, we increase the beam power—and astatine-211 production rate—without melting the target. The 25-particle microampere helium-4 beam—one of the world's highest beam currents for astatine-211 production in its class—is used in our

Azimuthally Varying Field (AVF) Cyclotron, a spiral-shaped particle accelerator built for use in a variety of research fields, ranging from nuclear physics to medicine.

We have also introduced a fast and efficient astatine-211 purification method that uses dry distillation. After collecting the irradiated target from the accelerator, we can simply heat it and the volatile astatine-211 separates from the remaining bismuth as a gas. We then attach the astatine-211 to a cancer-targeting molecular carrier, creating the radiopharmaceutical.

COMBATING CANCER

With a half-life of just 7.2 hours, the rapid decay of astatine-211 imposes significant restrictions on transportation time, limiting the delivery area. The larger the batch that we can make, however, the further we can transport it and still have a useful amount left once the sample reaches its destination.

With our improved astatine-211 production technique we can now distribute our product to many researchers in Japan. We currently support approximately 20 research groups with our astatine-211. In one recent highlight, our product was used for Japan's first clinical trial of the targeted alpha-particle therapy for thyroid cancer at Osaka University Hospital. This was the first time our product has been used for human treatment.

A second experimental astatine-211 radiopharmaceutical, also developed with Osaka University, will be tested in a human clinical trial for another cancer in 2024.

> Our latest advance deploys a production system based on a rotating liquid bismuth target. This innovation opens up the possibility of using even more powerful beams.

Increasing our astatine-211 production rate also means we can reduce the expense of these cancer drugs. The particle accelerator's running costs are very high, so if we can increase the production rate by using stronger beams, we can reduce accelerator beam time, which reduces drug development costs and, subsequently, drug prices. In addition, if we can produce more astatine in the same amount of bismuth, we can also increase the purity of the final shipped product, because the total amount of chemical impurities introduced during the chemical process remains the same.

For these reasons, we continue to develop improved methods for making astatine-211. Our latest advance deploys a production system based on a rotating liquid bismuth target. This innovation removes the need to keep the temperature very low, opening the possibility of using even more powerful beams.

CURRENT RESEARCH

In our liquid bismuth process, developed with the Metal Technology Company, a business based in Tokyo that produces advanced metal processing technology, the bismuth is placed in a tilted, rotating cup. As the cup is heated to 300–400°C, and spun at 2,000 revolutions per minute, the molten bismuth spreads to coat the wall of the cup due to centrifugal force. The liquid bismuth is then targeted with a powerful helium-4 beam.

In a further efficiency boost, the system has been designed so that we can collect the astatine-211 easily from the accelerator. As the astatine-211 turns onto a gas from the hot bismuth target, it is swept from the accelerator in a stream of helium carrier gas, passing via tubing into an adjacent lab where it is captured using a trap cooled to −196°C. So, the astatine-211 can be collected in a continual process as the molten bismuth is irradiated, or in a separate step post-irradiation.

We have currently installed this liquid bismuth system on one of RIKEN's powerful accelerators, called the RIKEN Ring Cyclotron, which is operating with a beam power of 25 particle microampere or more. In April 2024, however, we are planning to install the system on our most powerful instrument, the recently upgraded superconducting RIKEN linear accelerator (SRILAC).

As with RIKEN's original 1930s cyclotron accelerator, this upgrade was initially planned with fundamental research in mind. In its prior form, this linear accelerator was used in our synthesis of nihonium, one of our research center's greatest discoveries. To access even heavier new elements, we have upgraded this instrument by installing a new superconducting ion beam source and accelerator to increase the beam current and energy. Our target is to synthesize a new superheavy element, element-119, which has never previously been made.

With its very powerful particle beams, however, this accelerator should also be invaluable for the large-scale production of astatine-211. We are currently commissioning a new beamline on this apparatus for astatine-211 production based on our rotating cup technology, gradually increasing the beam current to until we reach about 100 particle microamperes.

With this advance, we will continue the strong dual tradition of developing accelerators for both practical and fundamental research at the RIKEN Nishina Center for Accelerator-Based Science.

HIROMITSU HABA
Director, Nuclear Chemistry Group and Superheavy Element Research Group, RIKEN Nishina Center for Accelerator-Based Science

Hiromitsu Haba received his Ph.D. from Kanazawa University in Japan in 1999. Next he worked at the Japan Atomic Energy Institute as a postdoctoral researcher, and then at RIKEN as a special postdoctoral researcher, research scientist, senior research scientist, and team leader. In 2018, he became director of the Radioisotope Application Research Group, then director of the Superheavy Element Research Group and later director of the Nuclear Chemistry Group at the RIKEN Nishina Center for Accelerator-Based Science. He is also a visiting professor at the Graduate School of Science and Technology at Niigata University, Japan. His scientific interests focus on nuclear and radiochemistry, with a particular speciality in the synthesis and chemistry of superheavy elements and the production and application of radioisotopes made using accelerators.

Promoting female researchers

At RIKEN, we are committed to diversity, and offer programs and measures to facilitate the active participation of talented women researchers and to promote their recruitment. In FY 2018, RIKEN launched a program named after an early Japanese female researcher, Sechi Kato, with the goal of nurturing female researchers who have a broad perspective and inquisitive mind, and who can shine in the international arena as world-class research leaders. Women researchers can apply for two RIKEN programs.

SECHI KATO'S IMPACT ➜

Most women weren't allowed to sit university exams in Japan in the early 20th century. As a result, the first woman employed at RIKEN, Sechi Kato (1893–1989)—a chemist who developed a method for spectrometric analysis of organic materials—was not a university graduate when she hired in 1922. But by 1931 Kato had become the third women to recieve a doctorare of science in Japan. In 1942, she was appointed a fully-fledged research scientist, performing work on airplane fuels. In 1951, Kato became the first female scientist to lead a RIKEN laboratory as a chief scientist, a position she held until 1954.

SECHI KATO PROGRAM FOR RIKEN HAKUBI FELLOWS PROGRAM

for positions starting up until financial year 2023

The RIKEN Hakubi Fellows Program, which was open for positions starting up until the end of financial year 2023, offered junior principal investigator positions for independent research by exceptionally talented researchers. The Sechi Kato Program was open to talented female researchers participating in this program.

Recently, two Hakubi Fellows Program members, ← **Erika Kawakami** at the RIKEN Center for Quantum Computing and Asuka Takeishi at the RIKEN Center for Brain Science, began participating in the Sechi Kato Program.

SECHI KATO PROGRAM FOR RIKEN ECL PROGRAM

for positions starting in FY 2024 and beyond

The Sechi Kato Program, which was initiated in 2018 under the RIKEN Hakubi Fellows Program, has been extended to the RIKEN ECL Program. The RIKEN ECL Program offers team leader and unit leader positions for female researchers. ECL researchers who are accepted into the Sechi Kato Program will receive up to ten million yen annually in research funds, in addition to the funds offered under the ECL Program.

Find out more at: www.riken.jp/en/careers/diversity/sechikato/

DIVERSITY PROMOTION FUND

In addition to the Hakubi/ECL programs, RIKEN has an initiative that offers additional research budget subsidies to newly appointed or promoted female principal investigators. These are researchers in managerial positions, such as **Catherine Beauchemin** ➜. The aim is to promote outstanding female-led initiatives at each RIKEN center and to support plans to improve the environment to enable female researchers to actively participate. in research activities.

RIKEN'S CENTERS AND FACILITIES

across Japan and around the world

WAKO (RIKEN's Headquarters)

Transformative Research Innovation Platform of RIKEN Platforms (TRIP)
- ● Center for Emergent Matter Science (CEMS)
- ● RIKEN Center for Quantum Computing (RQC)
- ● Center for Sustainable Resource Science (CSRS)
- ● Center for Brain Science (CBS)
- ● Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)
- ● RIKEN Nishina Center for Accelerator-Based Science (RNC)
- ● RIKEN Center for Advanced Photonics (RAP)
- ▲ RIKEN Cluster for Science, Technology, and Innovation Hub (RCSTI)
- ▲ Cluster for Pioneering Research (CPR)
- ◆ Radio Isotope Beam Factory (RIBF)
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

YOKOHAMA

- ● Center for Sustainable Resource Science (CSRS)
- ● RIKEN Center for Integrative Medical Sciences (IMS)
- ● Center for Biosystems Dynamics Research (BDR)
- ■ RIKEN Center for Computational Science (R-CCS)
- ▲ RIKEN Cluster for Science, Technology, and Innovation Hub (RCSTI)
- ◆ Genome Sequencing
- ◆ Nuclear Magnetic Resonance (NMR)
- ◆ Cryo-electron microscope
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

HARIMA

- ■ RIKEN SPring-8 Center (RSC)
- ◆ SPring-8
- ◆ SACLA

NAGOYA

KOBE

- ● Center for Biosystems Dynamics Research (BDR)
- ■ RIKEN Center for Computational Science (R-CCS)
- ◆ Animal facility
- ◆ Robotic Biology Prototyping Laboratory
- ◆ Supercomputer Fugaku

LEGEND

- ● Strategic Research Center
- ■ Research Infrastructure Center
- ◆ Large Research Infrastructure
- ▲ Research Cluster
- ▼ Information Research and Infrastructure

SENDAI

- ● RIKEN Center for Advanced Photonics (RAP)

TSUKUBA

- ■ BioResource Research Center (BRC)
- ◆ BioResource

TOKYO

- ● Center for Advanced Intelligence Project (AIP)
- ■ RIKEN Center for Computational Science (R-CCS)
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

KEIHANNA

- ■ BioResource Research Center (BRC)
- ● Center for Advanced Intelligence Project (AIP)
- ● Guardian Robot Project (R-IH)

OSAKA

- ● Center for Biosystems Dynamics Research (BDR)
- ◆ Supercomputer MDGRAPE-4A

Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network. RIKEN now supports five main research campuses in Japan and has set up a number of research facilities overseas. In addition to its facilities in the United States, RIKEN has joint research centers or laboratories in Germany, China, Malaysia, Singapore and other countries. To expand our network, RIKEN works closely with researchers who have returned to their home countries or moved to another institute, with help from RIKEN's liaison offices in Singapore, Beijing and Brussels.

For more information, please visit:
www.riken.jp/en/research/labs/ www.riken.jp/en/collab/research/

RIKEN RESEARCH

www.riken.jp/en

RIKEN 2024-019